

Melphalan Therapy in Myelomatosis

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Therapy of myelomatosis has always been rather disappointing. Even though urethane, first introduced by Alwall (1947, 1952), may give some really spectacular results, these are much too unpredictable, and the general consensus seems to be that the number of patients who tolerate the drug well enough is too small to allow successful therapy on a large scale.

Alwall's first patient lived for 40 months in good health before the final relapse occurred. She had a high plasma-cell count in the bone-marrow which disappeared completely on therapy, but her skeletal foci did not heal. She was on continuous urethane treatment during the whole period. Still more remarkable were the early results obtained by Saltzman and Borgström (1950) with the same drug. Their paper contains radiographs of the skull showing almost complete healing of the foci. The patient lived for only 20 months and then died of his disease. Some excellent results have been reported from the U.S.A. (Rundles, Dillon, and Dillon, 1950; Lutgens and Bayrd, 1951).

Reports from Russia (Blokhin, Larionov, Perevodchikova, Chebotareva, and Merkulova, 1958; Larionov, 1959) seem to indicate that a new antimetabolite called sarcosylsine (racemic) may be highly effective in the treatment of myelomatosis. In recent years we have been interested in problems of protein metabolism connected with the proliferation of plasma cells and lymphocytoid reticulum cells (see Heremans, Laurell, Martensson, Heremans, Laurell, Sjoquist, and Waldenström, 1961; Waldenström, 1962a). A number of patients having different types of myeloma proteins were seen in hope of finding a better treatment for their disease. Professor A. Haddow and Dr. D. A. G. Galton, of the Chester Beatty Institute, London, kindly helped us to obtain sufficient quantities of the compound called melphalan (L-bis-chlorethylamino-phenylalanine; L-sarcosylsine) for our therapeutic trials. The drug was first synthesized in 1953 by Bergel and Stock (1954), and is now manufactured by Burroughs Wellcome & Co. The warhead consists of a dichloroethyl-amino grouping (nitrogen mustard) and the amino-acid is thought to act as a carrier. To judge from the structure of melphalan, it is tempting to guess that it may act by interfering with protein synthesis.

Not very much has been published regarding the action of melphalan in myelomatosis. Swan (1962) reported partially good results after treatment of four cases of myelomatosis with melphalan. Bergsagel (1962) collected data from a joint enterprise in many clinics in the U.S.A. The patients were usually not followed for very long, and they were given short courses. Bernard, Seligmann, and Danon (1962) have published their experiences with the drug. The results of other workers will be reviewed in a monograph on myelomatosis (Waldenström, to be published).

Clinical Material

This paper is an account of our therapeutic trials at the General Hospital, Malmö. All patients except two were treated

and followed personally by me. It is evident that only observation over a very long period will give statistically reliable data. Our observations on 37 cases have lasted more than one year. We feel that both the subjective and the objective results of therapy have been quite encouraging in a number of these patients. Only four have died, after 12, 14, 20, and 34 months of the disease. Our total of treated cases is now 70. Four patients with macroglobulinaemia have also been treated with melphalan and two with chlorambucil ("leukeran") according to the same principles. These principles of drug administration have been to start with a rather intense course of 5 mg. of melphalan a day for 16, 20, or 25 days according to the patient's weight and condition (anaemia, etc.), then to stop the drug for one to two weeks while the leucocytes and platelets are investigated, and ultimately to continue with 2 mg. every day *ad infinitum* if no untoward effects are seen. We have thus followed the principles laid down by Galton for busulphan ("myleran") therapy and regard it as very important never to stop giving the drug if complications are not seen.

Among the malignant processes that are suitable for a quantitative analysis of the therapeutic effects obtained by anti-neoplastic agents, leukaemia, polycythaemia, and plasmocytoma occupy a unique position. In leukaemia and polycythaemia simple blood leucocyte and erythrocyte counts will often provide a reliable means of checking the effects of treatment. In most cases of plasmocytoma the quantitative analysis of the β - or γ -globulins might be thought to give valuable information regarding the influence of the therapeutic agent on the disease process. It is, of course, not an *a priori* certainty that a decrease in the pathologically increased globulins reflects a true amelioration of the disease, but as a working hypothesis this seems highly probable, and the approach is valuable because the effect of treatment as judged by changes in the x-ray picture is very slow. This fact is perhaps not realized by many workers, but the time-lag before healing of skeletal lesions after the first signs of metabolic normalization is probably about one year.

The division of patients with myelomatosis according to their types of prevalent globulins— γ_{88} or γ_{1A} in accordance with the recent terminology introduced by Waldenström (1962b)—might be expected to provide a convenient method whereby one could correlate the specific globulin abnormality of the patient to his response to therapy. This approach has been thoroughly investigated. A group in which the results of treatment are difficult to follow, however, is the one containing patients with a low content of serum γ -globulin. In this group an influence on the excretion of Bence Jones protein may be expected during therapy. Reliable quantitative determinations of Bence Jones protein have only been performed in some patients.

Our clinical material in Malmö with monoclonal hyper-globulinaemia—that is, M components—may be divided into three main groups: (1) patients with classical myelomatosis and

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a typical clinical picture; (2) patients having no signs of myelomatosis but a persistent benign—that is, non-progressive—monoclonal hyperglobulinaemia, described by Waldenström (1944, 1952) as essential hyperglobulinaemia; and (3) a few cases with increased macroglobulins. This last group should really not have been included in this paper, but we think that some of the results are rather interesting, and should therefore be discussed together with similar findings from the myeloma group (see Heremans *et al.*, 1961; and Waldenström 1962b).

The division of the treated cases—that is, those patients who have had at least one full course of melphalan—with respect to the nature of their globulin disturbances is as follows:

Whole Material (70 Cases)

64 cases of myeloma:
38 with increase in γ_{88}
7 with decrease in γ (Bence Jones)
2 with normal γ (Bence Jones)
16 with increase in γ_{1A} (β_{2A})
1 with increase in macroglobulin and a clinical picture of myeloma
2 cases of essential benign γ_{88} (with severe mental depression)
4 cases of macroglobulinaemia

Two patients have not been included, as they had only three days' treatment. Another had had only 40 mg. of melphalan when it was found that he had occult bleeding from an ulcer in the gastro-intestinal tract. Treatment was therefore stopped altogether.

Only eight myeloma patients in the city of Malmö were not treated during the period extending from August 1960 to December 1963. In four cases (K. H., G. S., L. H., and F. A.) the haematological status was such as to preclude therapy. Three patients died about two weeks after admission. One patient was treated with transfusions only. Another was not diagnosed clinically before he died (A. C.). The sixth patient had severe anaemia and a myeloma kidney (T. J.). He died in uraemia two weeks after admission without improvement of renal function. The seventh died rapidly in heart failure. The last of the eight has no pains and no skeletal lesions. She is still under observation. Without exception, all other patients who were diagnosed from the autumn of 1960 to December 1963—a period of more than three years—were treated. They were otherwise unselected. There may be a certain bias in our selection of the patients from other hospitals, but this problem will have to be discussed when we attempt to compare the true life-span in each group before and after treatment with melphalan.

Criteria of Successful Treatment

One of the most difficult problems connected with the assessment of new drugs is the lack of knowledge regarding the development of the untreated disease. Does a new preparation really prolong life? It is well known that, rarely, a patient with myelomatosis may get along remarkably well untreated. One striking result of melphalan administration is the rapid disappearance of pain. Is this "analgesic" effect of the new therapy real, or is it merely connected with the "cathartic" action of the treating physician's enthusiasm, the net effect of which is sedation and lowering of the patient's sensitivity to pain? In the case of myelomatosis, particularly, a surprising number of different therapeutic measures (urethane, radiology, ^{32}P , stilbamidine) have been quoted by various workers as having given almost immediate relief from pain, often without much evidence of effective influence on the disease process itself. This psychological factor can hardly be avoided, and we may even ask if it is not one of our most important tools in combating the effects of pain. On the other hand, it is not uncommon for patients with osseous metastases from a prostatic carcinoma to get relief of their pain very soon after the administration of oestrogens.

It is obvious that we must try to find other parameters for the objective control of therapeutic procedures. The level of serum acid phosphatase in prostatic carcinoma is an excellent example of such a parameter. Before entering upon this subject, however, I should like to state that the effect of melphalan therapy on the pain has been so rapid, and the resultant increased mobility of the patients so striking, that it is hard to understand how it could be due to anything but a purely somatic influence. The least far-fetched explanation would then be that "proliferation" of the plasma cells in itself causes pain from the adjoining tissues. This interesting problem will not be discussed any further. It seems probable, however, that the disappearance of pain, which allows the mobility of the patients to be nearer normal, should constitute an important healing factor so far as the osteoporosis is concerned. Pain is usually relieved at an early stage of treatment. After this, all patients have been allowed to move freely, but with caution. If the patient is suffering severe pain due to a recent fracture, this will, of course, not be relieved by melphalan.

We have chosen some more or less specific criteria to assess the effect of successful therapy. They are: (1) a decrease in a specific globulin fraction; (2) an increase in serum albumin and in normal "background" γ -globulin (which is often low and often associated with an increased tendency to develop infections); (3) a definite change in the x-ray picture; and, with great *critique*, (4) a change in the content of plasma cells on sternal puncture. Every haematologist with extensive experience in treatment of similar diseases knows how the results of sternal puncture may vary even when two punctures are performed on the same day. Only a general tendency—noted in a large series of cases or in single cases with multiple punctures—may be used as an argument in such discussions. Our results regarding this aspect will be treated by U. Axelsson (unpublished).

Control of Overdosage

It is very important to find the most reliable way of checking overdosage. It is quite evident that in order to obtain good results it is necessary to give doses large enough to produce a significant leucopenia. This is also true of urethane therapy. It is usually maintained that a pre-existing leucopenia should be regarded as a contraindication to treatment with cytostatic drugs. We have had some patients with very severe pains who had unusual leucopenia for cases of untreated myelomatosis (500–1,000 cells/c.mm.). During melphalan treatment, which was probably slightly more cautious than usual, the white-cell counts improved and there was never any thrombocytopenia. We thought it safer to put these patients on deltione therapy during the first part of their treatment. These are, however, exceptional patients, who showed great improvement both subjectively and objectively. Some patients did not develop a significant leucopenia (minimum 2,700 w.b.c./c.mm.) in spite of ordinary or even rather massive doses of melphalan; it is notable that one of these patients has shown a relatively slow—but steady—response with regard to his myeloma symptoms (see Fig. 1, Case K.O.). It is possible that he should have had more massive doses. On

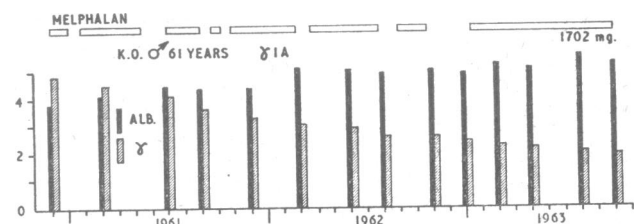


FIG. 1.—Patient K. O., aged 61, has shown a very remarkable type of response with continuous decrease in pathological globulin during the whole period of treatment. His general status is excellent.

the other hand, we have usually tried to avoid lowering the W.B.C. count below 1,000–1,500 and have generally terminated the treatment when such values occurred.

Three patients may have had too intensive therapy. In all three the condition was regarded as serious enough to warrant the additional risk of possible overdosage in order to afford the patients some relief.

Case A. N.—This patient had been treated successfully with urethane, but she was unable to tolerate the drug. She had a remission lasting for more than one year, but suffered a severe relapse. At that time we had had little personal experience with the correct usage of melphalan, and she was given a short and rather intensive course of 150 mg. in 12 days. She developed leucopenia and thrombocytopenia, but her pains disappeared; her serum albumin did not change, and her γ_{1A} -globulin value fell from 6.3 to 3.7%. She died after the course was finished and the post-mortem examination showed typical myeloma and a marrow that also contained numerous normal myeloid cells. It was evident, therefore, that she had not developed an aplastic marrow.

Case M. L.—This patient had a very high γ -globulin content (8%) in addition to a severe anaemia and, from the beginning, a marked thrombocytopenia. She also had signs of decompensated valvular heart disease. Eleven transfusions were given before and during melphalan treatment. During the first course of treatment her white-cell count fell to only 600; the count increased to 2,500 immediately after treatment was stopped, but her platelet count remained low (20,000) without signs of bleeding. After a pause, continuous treatment of 2 mg./day was instituted; she again developed leucopenia (800 W.B.C.) and the platelet count fell to 10,000/c.mm. All treatment was then stopped. Her serum albumin had increased a little and her γ -globulin had decreased. She died of acute pulmonary oedema in another hospital. A partial post-mortem examination was performed.

The third case is our only instance of probable severe melphalan poisoning.

Case A. P.—The patient, a woman born in 1903, had suffered pain referable to the hands and arms and loss of weight since October 1961. Bence Jones proteinuria was present. Sternal puncture revealed 95% plasma cells. There was some azotaemia and slight hypercalcaemia (5.2 mEq/l.). A carpal-tunnel syndrome was suspected, but the surgeons elected not to operate. Melphalan was given to a total of 115 mg. during March 1962. The white-cell count was 1,500, with 60% neutrophils and 84,000 platelets at the time the patient was allowed to go home for a pause in her treatment. She returned on 2 May with signs of agranulocytosis and azotaemia (120 mg./100 ml.) and died within two days. Post-mortem examination showed widespread myelomatosis, slight signs of myeloma kidney, and widespread necroses of the type seen in agranulocytosis. The patient also had a carcinoma of the pancreas with widespread thromboses in many organs. The carpal tunnels were not examined.

Agranulocytosis has also been seen in untreated myelomatosis (Vaughn and Raphael, 1956). It is, of course, difficult to judge the possible part played by melphalan in the fatal outcome in the first two patients, who were suffering from myelomatosis in a stage that is probably terminal if left untreated. In the case of M. L., the low platelet counts should, with our present-day knowledge, have induced us to stop treatment after the first course. In patient A. P. it seems possible, but not certain, that the fatal agranulocytosis was caused by the drug. We are at present inclined to use melphalan with great caution, if at all, in the severely anaemic patients.

As a general rule it may be said that the development of thrombocytopenia of less than 100,000 and of leucopenia below 1,000–1,500 should usually lead to temporary discontinuation of the medication if the condition of the patient is not very severe. It is interesting to note that low platelet counts and leucopenia tend to occur at the same time, but isolated low counts are also seen. Apart from the possible instances quoted, we have not seen any unfavourable results of melphalan treatment, and it must be pointed out that the preparation is extremely well tolerated subjectively. In no instance was bleeding thought to be associated with thrombocytopenia, with the possible exception of one patient having carcinoma of the

colon and liver cirrhosis and another who had nose-bleeds and a transitory purpura when her platelets were low.

We think it is necessary to make white-cell and platelet counts two or three times weekly during the initial high-dose stage. Later we have followed the development with weekly counts until a certain steady state has been reached, when counts are made at intervals of two to three weeks.

Space does not allow a discussion of the natural history of untreated myelomatosis. We have had an opportunity of following the protein patterns in a few of our untreated myeloma patients, and it has become evident that there is a steady increase in the specific hyperglobulinaemia in such cases; it would appear that this is one of the biological differences between the benign and the malignant types, even if exceptions are found. For a discussion of these problems see Waldenström (1962a) and a forthcoming monograph by me.

Therapeutic Results

An interesting and important question is: Are there any indications that certain biological types of myeloma are more resistant to treatment than others, or that they become refractory during treatment? If we try to group our patients according to the type of globulin produced, the first question cannot be answered. We have seen one patient (H. H.) whose elevated γ_{8S} -globulin showed remarkably little response to treatment with large doses of melphalan even though his osteolytic process was stopped. It may well be that the cryoglobulin character of this particular globulin was important prognostically. The patient was later treated with ordinarily sufficient quantities of urethane, but again without much effect on his globulin level. He was still in comparatively good condition after more than three years' treatment, which is unusual for a male (Fig. 2). On the other hand, some patients, who also had typical γ_{8S} myelomas, had the most rapid responses of all (Fig. 3).

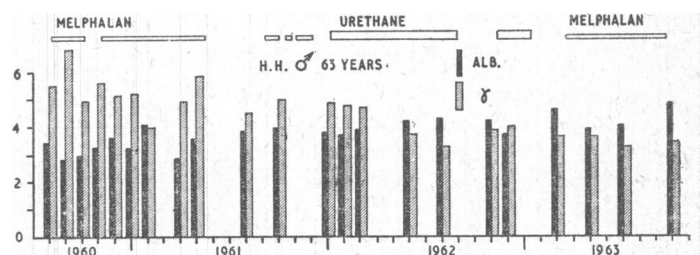


FIG. 2.—Patient H. H., aged 63, has shown comparatively little response as regards γ -globulin but is much improved clinically. No real difference in response to melphalan or urethane in big doses. His general status has remained fairly good. He was walking around but needed analgesics.

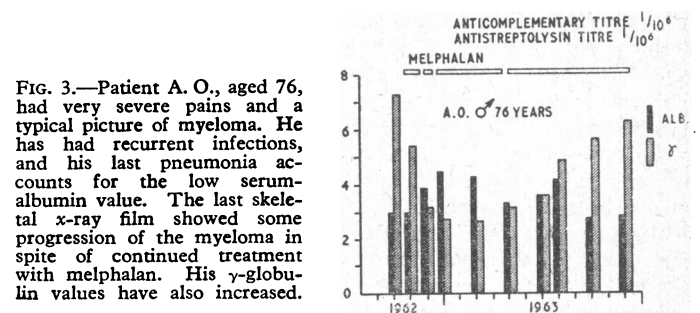


FIG. 3.—Patient A. O., aged 76, had very severe pains and a typical picture of myeloma. He has had recurrent infections, and his last pneumonia accounts for the low serum-albumin value. The last skeletal x-ray film showed some progression of the myeloma in spite of continued treatment with melphalan. His γ -globulin values have also increased.

Fig. 4 shows that insufficient dosage may give a transitory response whereas more massive dosage brings further improvement.

A remarkable finding in one of these patients was the presence of increased quantities of plasma cells in her blood. Traces of serum albumin and globulin were present in the urine. The administration of only 130 mg. of melphalan caused an almost

complete remission with respect to the serum globulin, and she was the only patient we have seen whose red cells increased as much as 1,500,000. In spite of this strong effect, her white-cell count never fell below 1,000/c.mm. and her platelets never below 100,000. After this very remarkable remission the patient developed reticulum-cell sarcoma with extensive Bence Jones proteinuria and died. It would appear that a different

The normoblasts thus seem to be comparatively resistant to melphalan. On the other hand, it is noteworthy that, except in one of our most spectacular cases (B. A.), there was rarely any real increase in the red-cell counts. It would be hard to explain the mechanism for this consistency solely on the basis of inhibition of the erythropoietic system by the drug. It is also remarkable that the effect of the drug on protein synthesis of another kind—that is, albumin synthesis (Table II)—should be enhancing in those patients in whom the formation of the myeloma globulin is strongly inhibited. It is possible, however, that the increase in albumin is not only the result of increased synthesis.

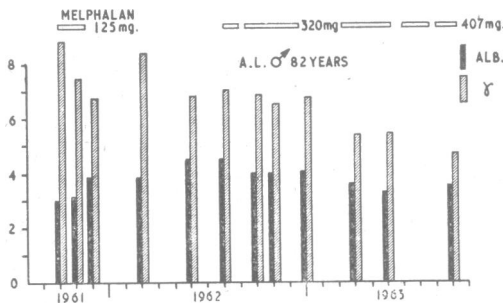


FIG. 4.—Patient A. L., a man aged 82, showed slow effect of melphalan on serum globulin but only slight progress of the skeletal process on the x-ray picture. Electrophoresis demonstrated a very rare biconal picture initially. With melphalan the smaller component has disappeared and the bigger has decreased from 6 to 4.5 g./100 ml.

clone of cells arising from the reticular system had become malignant. Between these two extremes we find the main group. Several patients with γ_{1A} myeloma have responded very well both chemically and clinically to treatment. One such patient even showed signs of skeletal healing, but in spite of this she suffered a serious relapse when her dose was lowered because of thrombocytopenia. Her total dosage had been 700 mg. in 14 months. Another patient with γ_{1A} myeloma responded to 450 mg. with a continued lowering of the globulins during one year's treatment; there was also a very marked subjective improvement. The results in 49 cases are shown in Table I.

TABLE I.—Results of Melphalan Therapy in 49 Patients

Decrease in M Comp. %	25 γ_{SS}	12 γ_{1A}	4 γ_{IM} (3 Macro)
0	2*—5†	1†	—
5-20	3†	—	—
21-40	6	2	2
41-60	5	8	1
61-80	1	1	—
>80	3	—	1 (Myeloma)
No M-comp.	8		

* Essential γ_{SS} .
† Inadequate therapy in one patient from each group.

It seems likely that the patient (H. H., Fig. 2) with cryoglobulinaemia had a relative resistance from the start; we have seen some patients become refractory when treated continuously with large doses. Also, the only patient with pyroglobulins was remarkably resistant (A. L., Fig. 4). Our present feeling is that the treatment should never be stopped for any reason other than signs of overdosage. Some patients have been treated with repeated full courses. Patient A. L. probably responded about as well to the second as to the first course. If a new clone of malignant cells had developed during treatment you could suppose it to be resistant to the same drug. Therefore it seems more likely that we are dealing with the same clone of malignant cells throughout the period of therapy. Two patients have been biconal.

During the summer of 1961 we wished to give some patients a respite from their repeated blood examinations, and I was also interested in seeing whether the erythrocyte count would rise when melphalan was temporarily stopped. Possibly two or three patients increased their erythrocyte counts (500,000) during this time. It is quite remarkable that we have seen few patients whose anaemia worsened as a result of treatment.

TABLE II.—Serum Albumin. Effect of Melphalan

	γ_{SS}	γ_{1A}	γ_{IM}	$\gamma \downarrow$
Normal before	9	6	1	(7)
Decrease	1	—	—	—
	(3.7—3.1)			
Increase to normal from <3.0%	6	—	—	—
„ 3.0>4.0%	8	4	—	—
„ 2.9—3.8%	1	—	—	—
	(Glob. 6.3—1.1)			
Recent or short courses	—	—	—	—

One of the most serious aspects of myelomatosis is, of course, the impairment of normal γ -globulin synthesis; this finding seems to be present in almost every patient investigated for this condition. We believe that the intense proliferation of one clone of plasma cells may lead to inhibition of the development of other normal clones. It would seem likely, therefore, that the hypogammaglobulinaemia would be favourably influenced by the reduction of pathologically increased γ -globulins. Such has rarely been the case, however, and we must ask ourselves whether proliferation of one plasma-cell clone causes a more or less irreversible inhibition of all or some of the others. Even in benign monoclonal hypergammaglobulinaemia the level of “normal” γ -globulin is definitely low. These relationships seem to have important biological implications and will therefore be studied in different conditions.

The salient question is, of course, whether a reduction in γ -globulin formation reflects a reduced vitality in the myeloma cells which would lead to a disappearance of the destructive proliferation and ultimate healing of bone lesions. This is not necessarily true. It may be possible that this special drug, by interfering with the function of the γ -globulin templates, influences this part of cell metabolism without “killing” the cells. Our results definitely indicate that the drug—even when strongly depressing the formation of “pathological” γ -globulins in the myeloma cells—does not interfere with the synthesis of albumin, as the level of this protein increases markedly during therapeutic depression of M-component γ -globulins.

Perhaps the most interesting problem concerns the formation of normal antibodies. Their level is often depressed in myeloma (Waldenström, Winblad, and Hällén, 1964, *Acta med. Scand.*, in press), and we have never seen it rise during successful melphalan treatment. It would of course be interesting to know whether other γ -globulin-forming cells are also affected by melphalan. We know that both γ_{1A} and macroglobulin formation are inhibited not only in γ_{SS} myeloma but also in essential benign monoclonal γ_{SS} hypergammaglobulinaemia. We have treated two patients with this condition who suffered from severe mental depression with melphalan. Our hope was that the psychiatric condition could in some way be related to the γ -globulin formation as we have several other patients with this combination. Our dosage of melphalan was very slight in one patient and we did not see any therapeutic effects of the course. The other patient was treated twice. Her psychic status remained unchanged but her bone-marrow was profoundly affected temporarily. There was little influence on the γ -globulin values except on one occasion six months after stopping melphalan. This may possibly be due to analytical errors. The development of her condition is seen from Fig. 5.

Ideally, one should be able to evaluate the results of therapy by observing a complete or partial regression of the skeletal lesions on x-ray examination. This process can best be followed on radiographs of the skull, where the size of the lesions can be measured exactly and the number of foci can be counted. On the other hand, the more diffuse skeletal processes, such as those that result in a porotic condition of the vertebral bodies, are difficult to measure quantitatively. It must also be remembered that healing of such bone processes is always extremely slow. Patients with so-called osteoporosis (osteopenia) from different causes ("senile," malabsorptive) never show normalization of their spine, as the accompanying compression fractures are, of course, irreparable. The same holds true for patients with Cushing's disease, who still demonstrate x-ray changes in their spine many years after an otherwise successful operation. We have therefore not tried to follow the condition of the spine as closely as that of the pelvis and the cranium. Some patients have readily delimited lesions in humeri, femora, or elsewhere. These have then been the subject of follow-up examinations.

2.8 g./100 ml., but no skeletal symptoms. X-ray picture negative. His sternal puncture disclosed a marrow rich in plasma cells. As he did not suffer from any pains and he had no anaemia, it was thought best to observe his course before starting melphalan treatment. In the meantime he developed severe back pain but did not consult his usual doctor, and was treated with massage. Six months later he was found to have several fractures of vertebrae and suffered severe pains. Melphalan was given with excellent results—a decrease in his pain and a marked drop in globulins from 3 to 0.7 g./100 ml. At the same time his serum albumin increased from 4.4 to 5.3%, whereas his red-cell count fell from 4,200,000 to 3,400,000. He was very happy with the result, but of course it would have been much better had he not been allowed to develop the fractures of the spine. He was last examined in August 1963.

I have received information from two colleagues regarding the status of two patients who were much improved during treatment.

E. B., a woman born in 1910, has suffered from ulcerative colitis since 1951, with few clinical symptoms. In January 1961 myeloma was suspected. Later, destruction of the pelvis and both

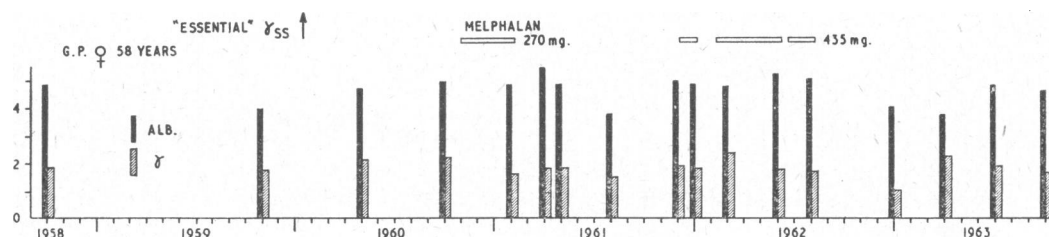


FIG. 5.—Patient G. P., a woman aged 58.

It is remarkable that even the patients who have been followed for about two years or more rarely show signs of actual healing. In eight patients it could be said that the *status quo* has been maintained for a long period. This is definitely rare in untreated patients. Only five patients showed signs of regression of bone lesions. In some of these, treatment had to be stopped, after which further x-ray progression of the disease was noted. In others, slight progression of the lesions in one part of the skeleton was noted, while there was regression in other parts. This has also been observed in urethane treatment. In a large number of patients the treatment has not lasted long enough for any changes to occur. Seven patients showed progression of the bone processes, often because continuous melphalan treatment had to be stopped, owing to external circumstances or, in some cases, because there was a danger of complications arising from the therapeutic depression of the white cells or platelets (Table III).

femora occurred, accompanied by severe pains. Melphalan therapy was started in January 1962, with excellent effect on the serum proteins. The M component dropped to 0.7% and the background γ globulin increased. In April 1962, after trauma, there was a left-sided femoral fracture. In November 1962 the red-cell count was 3,300,000 white-cell count 9,000, and platelets 614,000. A new course of melphalan started in January 1963 is being continued.

Another patient was treated with only one course of melphalan without any continued administration of the drug. She had a remission lasting for three years, with a decrease in the β fraction from 6.1 to 1%. She then suffered a relapse with 3.7% of the M component and is now being treated with a new course of melphalan. A big tumour protruding on her cranium disappeared.

The mechanism of the bone destruction in myelomatosis is not, of course, well understood. It may be thought that some plasma cells have an innate capacity for osteoclasia—that is, that they contain the enzymes that are capable of destroying bone. In some patients the plasma cells may have a tendency to grow in groups and form "tumours" that give the typical foci. In other instances there is more or less diffuse growth, which leads to the x-ray picture of osteopenia. Many authors have stressed the fact that there must be little osteoblastic activity in myeloma patients, as the alkaline phosphatase values are rarely, if ever, elevated. In Paget's disease, on the other hand, there must be both osteoclasia and bone formation. The alkaline phosphatase level is high and there is a remodelling of the bone rather than a process involving progressive bone destruction.

Another way of looking at the same problem would be to say that bone destruction occurs only as the result of local pressure, just as an aneurysm is able to erode bone without any cell infiltration. The fact that the bone pains disappear very rapidly after institution of melphalan treatment might be explained in this way by assuming that the "turgor" of the plasma-cell tissue decreases. It is interesting that hypercalcaemia—if present—also disappears rapidly.

However this may be, it is evident that the healing tendency in myelomatous bone after melphalan is not very marked, even when other parameters seem to indicate a strong influence on the malignant cells. We should not forget, however, that

TABLE III.—Skeletal Changes in X-ray Picture

Progression (2 γ_{1A} , 9 γ_{8S})	11*
Status quo (3 γ_{1A} , 1 γ_{8S})	4
Regression (1 γ_{1A} , 7 γ_{8S})	8*
Too short courses	19
Not followed	3
No skeletal lesions (Low glob.) (3 γ_{1A} , 4 γ_{8S} , 1 γ_{1A})	8

* Progression and regression occurring simultaneously in some patients.

A number of patients in whom we have started treatment during the past year have not shown any skeletal lesions at all. My initial policy had been not to treat patients who showed no signs of bone destruction and pains, but this was reversed after we had some experience with the manner in which rapid bone destruction can occur during an observation period. With our present-day knowledge, I would be inclined to say that patients with clear-cut myelomatosis—that is, a high monoclonal globulin and a marked medullary plasmocytosis—should be treated at once, before skeletal symptoms arise. This is especially true of male patients, in whom the prognosis is obviously much poorer than in females.

The following is an illustration of the dangers that may arise from therapeutic procrastination in melphalan therapy.

A man, born in 1907, was seen, in consultation, from another hospital in September 1961. He then had a high γ_{1A} fraction of

fractures may heal quite well in myelomatosis. The phenomenon has been observed many times and indicates that osteoblastic activity may be sufficient.

Only future observations will give us material for the most important discussion—that is, that which concerns our chances to inhibit bone destruction in patients who have clear-cut myelomatosis without skeletal symptoms. Since a positive x-ray picture is one of our most reliable arguments for the diagnosis of myelomatosis, it is difficult to find enough such cases.

Regarding the treatment of leukaemia, it has been stressed repeatedly that it is easy to accomplish a decrease in the number of white cells, but that this should be followed also by an increase in red cells as well as in weight and in well-being. We may ask if the treatment of myelomatosis may ever bring about a cure of the very severe anaemia which is often present. The data in the present series are given in Table IV.

TABLE IV.—Erythrocytes During Melphalan Treatment

21 patients: No more than 10% difference.
12 patients: Decrease more than 10%, usually slight
4 patients more remarkable for increase (2.1—3.2, 2.2—2.8, 1.7—3.6, 2.4—2.9)
In some instances development could not be judged (bleeding, transfusions, short course, etc.)
No patient showed normalization of red cells during treatment
In several patients values increased during pause in therapy

In some patients the anaemia completely dominated the clinical picture before treatment. This is especially true in the following case.

H. S., woman born in 1885, had a very high E.S.R. (78 mm./1 hr.) and an M component (γ_{5s}) of 4.7 g./100 ml. She had no leucopenia, but demonstrated slight thrombocytopenia before treatment.

Contraindications for Starting Treatment

It is impossible to tell yet whether there are any fixed rules in this respect. Using the levels of red and white cells and platelets as a guide against overdosage, I had usually, in the intermediate part of the programme, excluded patients who needed repeated transfusions. The fact that we rarely saw a really substantial rise in haemoglobin has, of course, been an argument in the same direction. Subsequently, however, we have treated some severely anaemic patients quite successfully, at least temporarily. Another important parameter, the γ -globulin level, gives no guide regarding the results if the level is low. We had therefore refrained from treating such patients until we became interested in the study of Bence Jones proteinuria. Most of these patients are excreting large quantities of protein in their urine, and consequently are apt to suffer from myeloma kidney. For this reason we have tried to avoid treating one patient with severe kidney damage. Another patient with very severe azotaemia (N.P.N. 200 mg./100 ml.) was treated with large quantities of fluid until his renal output increased and his azotaemia was abolished. He then developed hypercalcaemia and temporarily responded well to steroids and melphalan, as reflected by a decrease in the serum M component and an improvement in his general condition. His anaemia was very severe, however, and melphalan had to be stopped. He died anaemic. We do not regard azotaemia as an absolute contraindication to treatment any longer, but we feel that the renal insufficiency should be treated before melphalan therapy is instituted. The presence of atypical amyloidosis may well be a contraindication to therapy, as we saw no beneficial results from treatment in one such patient who died rapidly from heart failure, azotaemia, and progressive anaemia.

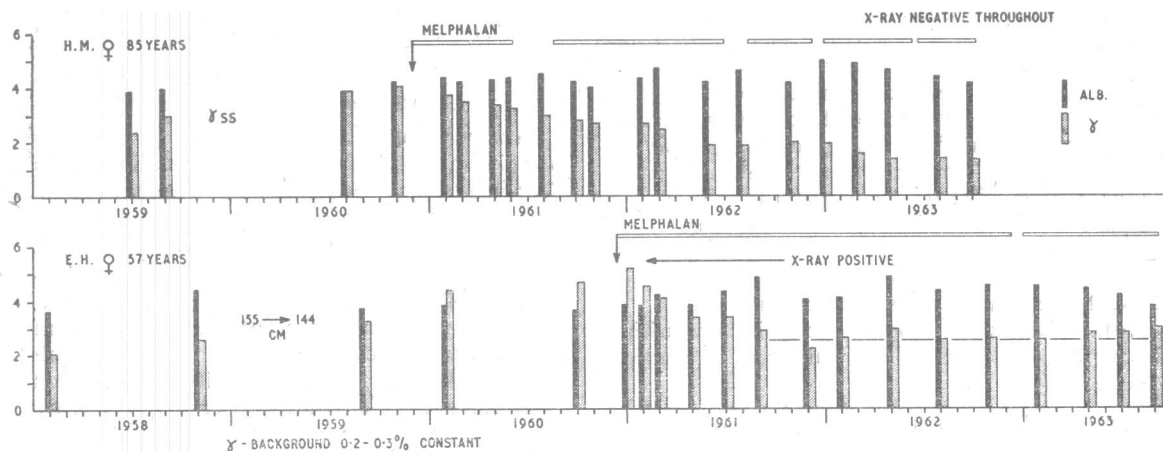


FIG. 6.—Changes in serum proteins before and after melphalan treatment in two patients with myeloma. In patient H. M., a woman aged 85, there is practically continuous decrease in the M component during melphalan treatment. In patient E. H., a woman aged 57, it seems as if the values had levelled off just below 3 g./100 ml. after a rapid initial response. Both patients showed continuous increase in γ -globulins before treatment as is characteristic of myeloma. In E. H. "normal" background γ -globulin could be determined accurately. It remained low and constant even in remission.

Her skeletal picture was normal. Her first sternal puncture showed only 6% plasma cells on 25 April 1962; therefore she was not treated with melphalan. A repeat puncture on 8 October disclosed 26% plasma cells, and the diagnosis of myelomatosis was established. She was given a short course of melphalan, 100 mg., and her white-cell count fell to 2,000, her platelets to 50,000, and her red cells to 1,400,000/c.mm. We therefore stopped the treatment and gave her repeated blood transfusions and prednisone. This had a very good influence on her general status and she was being treated as a case of aplastic anaemia, receiving about 1,250 ml. of blood per month. She had not developed any skeletal signs up to the spring of 1963, and it would appear that she had not suffered from any symptoms of myelomatosis other than the M component and anaemia. She did not excrete Bence Jones protein.

Our material includes several other severely anaemic patients. In one or two cases we have had to stop melphalan treatment and have tried steroids instead, but never with any real success.

Fig. 6 shows continued increase in monoclonal hyperglobulinaemia followed by continuous decrease after melphalan treatment in two cases. The first patient (H. M.) had a high plasma cell count but no osteolytic foci at any time. She had a high titre of thyroid antibodies. The second patient (E. H.) showed in principle the same development but her vertebrae showed multiple collapses with a decrease in stature of 7 cm. Melphalan reduced the M component considerably, but a steady state seems to have been reached during the last 18 months.

Summary

Seventy patients have been treated with melphalan. Two had essential benign monoclonal hyperglobulinaemia with severe mental depression. They had comparatively short courses of

melfalan with some decrease in γ -globulins but no influence on the depression. Four patients had macroglobulinaemia. One was treated for only a short time for external reasons. Another had a good response as regards macroglobulins. He lived in an old people's home, where he fell and broke his hip, finally dying from old age after melfalan had been discontinued for a long time. Two patients had excellent responses both clinically and biochemically on continuous treatment. Nine patients with myeloma had low γ -globulin values. Most of them had marked excretion of Bence Jones protein. Five died during the treatment but two had only short courses. Four are alive, three in rather good condition. In two other patients there was not very much influence on the γ -globulin values, which were not much increased before treatment. Clinically these patients responded well to treatment and are alive and active after 10 months on melfalan. Nine patients had excellent initial response with later relapse so far as γ -globulin is concerned. Only one of these patients has been taking the drug continuously. His general condition is excellent but his γ -globulins have returned to the same level as before treatment. All the others have had clinical relapses. Five have died from their disease after the stopping of treatment because of haematological or other complications. Of 34 patients on continuous treatment, 31 showed continued good results, both clinically and biochemically. Two have died from intercurrent cardiac disease. One died from reticulum-cell sarcoma and myeloma in spite of very low γ -globulin values. The others are in clinical and biochemical remission. In seven patients the treatment has been started recently and the influence on the γ -globulin values cannot therefore be judged. Seven patients have had only short courses because of complications. Only two are alive.

Twenty-two treated patients have died; in six the treatment was too short. Among these there was one patient with liver cirrhosis and cancer of the colon. Two severely anaemic persons were treated for hypercalcaemia. Three died from cardiac disease. Eight died from myeloma in spite of a full course (five or six had good initial results). One patient had amyloid. One had a fatal relapse after stopping treatment during a voyage to the U.S.A. One developed agranulocytosis; she also had a pancreatic carcinoma.

In conclusion, it may be said that we have not seen any patient with marked increase in M components where we have

been able to give a full course of the drug who did not respond clinically and biochemically to the treatment. Severe anaemia, leucopenia, and thrombocytopenia are contraindications against starting treatment. In two such patients with hypercalcaemia this symptom was corrected but the ultimate result was fatal. It seems probable that patients with marked excretion of Bence Jones protein have a poorer prognosis than others. Our results indicate that stopping of treatment may result in severe relapse. Continuous treatment with 2 mg. every day or every other day should be given indefinitely if no haematological complications arise.

Pains usually disappear rapidly. Serum albumin increases with few exceptions. Anaemia may improve but was never healed; increasing anaemia has also been seen.

The drug seems to be very potent if given in sufficient doses. It is much superior to urethane. Comparisons with cyclophosphamide have not been made.

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Leucine-induced Hypoglycaemia and Oral Hypoglycaemic Drugs

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The amino-acid L-leucine produces hypoglycaemia in some infants (Cochrane *et al.*, 1956) and in some patients with pancreatic β -cell tumours (Schwartz *et al.*, 1959). This hypoglycaemia is associated with increased levels of circulating insulin or insulin-like activity (Yalow and Berson, 1960; Butterfield *et al.*, 1960; Weisenfeld and Goldner, 1961), but, apart from this, little is known of the mechanism(s) underlying leucine-induced hypoglycaemia. Fajans *et al.* (1960, 1963) have demonstrated that normal individuals treated with chlorpropamide become sensitive to the hypoglycaemic effect of

leucine and that the hypoglycaemia is again associated with increased levels of circulating insulin, as measured by an immuno-assay method. This new information led us to investigate the effects of two other oral hypoglycaemic agents—tolbutamide, another sulphonylurea derivative, and the biguanide, phenformin. Cochrane (1960) suggested that leucine might normally play some part in the release of insulin, and that susceptible infants were simply hypersensitive. There is some evidence (Butterfield *et al.*, 1962) that tolbutamide affects the uptake of certain amino-acids, including leucine, by human forearm muscle. It is possible, therefore, that the sensitizing effect of the sulphonylureas is due to enhanced uptake of leucine by the islets, and an attempt has been made to study this in the rat.

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