Heavy cigarette smoking was associated with both cor pulmonale and degenerative heart disease, but the association might have occurred by chance.

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MANNOMUSTINE IN TREATMENT OF LEUKAEMIAS, POLYCYTHAEMIA, AND MALIGNANT DISORDERS

BY

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Since the introduction of β -chloralkylamines as therapeutic agents for the treatment of leukaemias and the reticuloses (Gilman and Philips, 1946; Wilkinson and Fletcher, 1947) many derivatives and analogues have been examined. Those in more or less regular use at the present time have been considered previously (Wilkinson, 1953, 1955a, 1955b; Scott, 1958). Another cytostatic preparation that has been tried more recently is mannomustine (1:6-bis(β -chloroethylamino)-1:6-desoxy-D-mannitol dihydrochloride; B.C.M.; "degranol"), a substance synthesized by Vargha as one of a series of compounds linking the actively cytotoxic chemical group β -chloroethylamine with a naturally occurring substance, mannitol; it was thought that this would pass more readily through the cell membrane and therefore have a greater selectivity (Vargha *et al.*, 1957).

Mannomustine is a white crystalline compound readily soluble in water, and, although it remains stable for at least 24 hours, it should preferably be freshly prepared

immediately before injection. There are a few reports of the therapeutic trial of this substance by Sellei *et al.* (1956) and by Sellei and Eckhardt (1958) at the National Oncological Institute, Budapest.

Through the kindness of Messrs. Leda Ltd., generous supplies of mannomustine have been made available to us. We report here our preliminary results with this drug in 45 patients having polycythaemia, leukaemias, reticuloses, or malignant disease.

Dosage and Control

Mannomustine was supplied in ampoules containing 50 mg. of the dry crystalline substance; for use the contents of the ampoule or ampoules were dissolved in either physiological saline or ascorbic acid solution (10 g./100 ml.); a convenient strength was 10–20 mg. of mannomustine per ml., although concentrations of 25–40 mg./ml. have been given without the development of thrombophlebitis. It was given intravenously in most cases, but we have also injected the solution intrapleurally when there has been a massive or persistent pleural effusion.

Since the administration of doses as high as 200–500 mg. in one injection led to the much greater frequency and severity of toxic reactions, we later restricted the maximal single dose to 100 mg. daily or on alternate days, and this was found to be the most satisfactory dosage scheme. The required total dosage varied from patient to patient and with the particular disease, as we indicate later.

Diagnoses were made on the usual basis of history, clinical findings, and examination of peripheral blood and bone marrow in the leukaemias and polycythaemia, and in addition by gland biopsy in the reticuloses. Haemoglobin levels and total white blood cell and platelet counts were measured daily and full blood counts at weekly intervals on in-patients and full blood counts were taken at each out-patient attendance.

Chronic Myeloid Leukaemia (12 Cases)

Twelve patients with chronic myeloid leukaemia were treated with mannomustine (see Table I). Nine of these had had no previous antileukaemic treatment, while the remaining three (Cases 10, 11, and 12) had previously received busulphan ("myleran").

In general it was found quite satisfactory to give in single intravenous doses of 100 mg. an initial total course of 800–1,000 mg. when the initial white-cell count was 80,000 to 150,000/c.mm., and of 1,200–1,800 mg. when the initial white-cell count was over 200,000/c.mm. Subsequent doses were determined according to the haematological responses obtained.

In all patients moderate symptomatic improvements were noted, and were usually most pronounced two to six weeks after the beginning of treatment. In five patients this could be attributed partially to blood transfusions given. The livers were enlarged initially in 10 patients, 8 of whom showed moderate or marked reductions in size, maximal reductions occurring within six to eight weeks. The spleens were enlarged in all but one patient (Case 12); there was marked reduction in size in five patients; slight or moderate shrinkage in four others, and the spleen became palpable in only two (Cases 2 and 5). One patient (Case 10) with gross splenomegaly and a white blood cell count of 31,000/c.mm. was given mannomustine in an attempt to reduce the size of the spleen. Only slight reduction

occurred, but the patient did not require further anti-leukaemic treatment before she died, nine months later.

The haemoglobin levels increased significantly in seven patients at an average rate of 2.5 g./100 ml. in 6.7 weeks (3-12 weeks). The initial total white-cell count varied from 27,000 to 508,000 per c.mm.; the lowest values were usually recorded after four to six weeks from the beginning of treatment (see Table I). Further rises to higher levels usually occurred within a further four to five weeks, with the exception of one patient (Case 1) who is still in remission after eight months. There was no reduction in the percentage of early myeloid cells in three patients, while in the remaining nine the percentage of primitive cells varied directly with the total white-cell count. The greatest reduction was noted in the "blast" forms, the less immature early myeloid cells being more resistant. Only two patients developed thrombocytopenia, both symptomless and transient. Further courses of mannomustine were given in six cases (Nos. 2, 3, 5, 6, 9, and 12). The response to these second courses was disappointing in all six, three showing no response, while the remaining three, after a preliminary improvement, relapsed four to five weeks later.

Case 1.—A 63-year-old woman with chronic myeloid leukaemia was given mannomustine to a total of 800 mg. (100 mg. on alternate days). The white blood cells fell from 117,000 to 1,050/c.mm. in four weeks. Simultaneously the platelets fell from 256,000 to 30,000/c.mm. and the haemoglobin from 9.2 g./100 ml. (62%) to 5.9 g. (40%). She was given blood transfusions and prednisolone, 40 mg. daily, and within seven days the white blood cells and platelets had risen to normal levels. Four weeks later the white blood cells were 23,000/c.mm. and a further 50 mg. of mannomustine was given. The white blood cells remained below 20,000/c.mm. for 36 weeks without further treatment. There was a 25% reduction in the size of the liver and the spleen over the first 11 weeks, but no further change occurred.

Case 2.—A 54-year-old man with chronic myeloid leukaemia had a moderately enlarged liver and spleen; total white blood cells, 151,000/c.mm.; haemoglobin, 8.6 g./100 ml. (58%); and platelet count 250,000/c.mm. He was given mannomustine, 100 mg. daily, to a total of 1,200 mg. In six weeks the white blood cells had fallen to 4,600/c.mm., haemoglobin rose to 11.1 g. (75%), and the liver and spleen were not palpable. The platelet count remained above 150,000/c.mm. He relapsed four weeks later, the spleen and liver enlarging and the total white blood cells rising to 119,000/c.mm. A further course of 750 mg. of mannomustine was given, with partial regression of liver and spleen and a fall in the white blood cells to 34,000/c.mm. He again relapsed four weeks later, and was subsequently controlled on busulphan.

Seven of the 12 patients (Cases 2, 3, 4, 5, 7, 8, and 9) were subsequently adequately controlled on busulphan: three (Cases 6, 10, and 12) died in an acute myeloblastic phase. Case 1 has not required any further antileukaemic treatment, and one patient (Case 11) who had previously become resistant to busulphan has been treated subsequently with demecolcine.

TABLE I.—*Effect of Mannomustine in Chronic Leukaemias*

Case No.	Age and Sex	Total Dose mg. (mg./kg.)	Before Treatment		After Treatment			Duration of Response (Weeks)
			Clinical Condition	W.B.C. 10 ⁹ /c.mm.	Clinical Condition	W.B.C. 10 ⁹ /c.mm.	Weeks	
Chronic Myeloid Leukaemia								
1	63 F	850 (16.7)	Poor S++++ L+++	117	Fair† S+++ L++	1.05	4	36*
2	54 M	1st course 1,200 (17.3)	Fair S+++ L++	151	Good S 0 L 0	4.6	6	4
		9 wks. later 750 (10.4)	Fair S++++ L++	119	Fair S+++ L+	34	5	4
3	37 F	1st course 1,200 (22.6)	Fair S++++	451	Fair S+++	139	6	3
		4 wks. later 1,300 (24.4)	Good S+++	338	Good S++++	174	4	—
4	26 M	1,300 (21.1)	Fair S++++ L+	482	Good S+++† L 0	44	6	2
5	59 F	1st course 1,000 (20.4)	Poor S+++	154	Fair S 0†	21	5	14
		10 wks. later 400 (8.2)	Fair S+	72	Fair S+++	114	2	—
6	58 F	1st course 1,100 (20.4)	Fair S++++ L+++	257	Fair S+++ L+++	52	6	5
		10 wks. later 1,400 (25.3)	Fair S++++ L+++	109	Fair S++++ L+++	32	6	4
7	39 M	1,400 (26.7)	Fair S+++ L+	259	Good S+++ L 0	40.4	3	3
8	53 F	800 (16.0)	Good S++++ L+	80	Good S+++ L 0	12	7	7
9	45 M	1st course 1,800 (30.0)	Poor S++++ L++	508	Fair† S+ L 0	27	6	2
		8 wks. later 1,000 (16.6)	Fair S+++ L+	212	Fair+ S+++ L 0	181	6	—
10	49 F	1,200 (21.8)	Poor S++++ L++	31	Poor S++++ L+	4.25	4	—
11	52 F	1,000 (13.8)	Good S++++ L+++	160	Good S+++ L++	33	4	1
12	27 F	1st course 150 (2.3)	Good L+	27	Fair† L+	8.9	9	4
		5 wks. later 600 (9.5)	Fair L+	225	Fair L+	28	3	5
Chronic Lymphatic Leukaemia								
13	57 M	1,200 (21.4)	Poor S+++ L+++ P.G.+++ M.G.+++	180	Fair S+++ L+++ P.G.+ M.G.+++	150	3	—
14	62 F	700 (9.3)	Good S+ P.G.++	168	Good S 0 P.G. 0	4.3	3	40*
15	57 M	700 (9.0)	Good S+ P.G.++	262	Good S+ P.G.+	22.7	2	18*

S = Size of spleen. L = Size of liver. P.G. = Peripheral glands. M.G. = Mediastinal glands.
* Continuing. † Given blood transfusions.

Chronic Lymphatic Leukaemia (3 Cases)

Three patients with chronic lymphatic leukaemia were treated with mannomustine (see Table I). One patient (Case 13) was in poor general condition before treatment, having considerable enlargement of liver and spleen and widespread involvement of all the lymph nodes. The other two patients were in reasonably good general health with moderate enlargement of lymph nodes and barely palpable spleens. The initial total white-cell counts varied between 168,000 and 262,000/c.mm., while the platelet counts were between 195,000 and 218,000/c.mm.

The responses to treatment varied considerably; in spite of a total dose of 1,200 mg. given in Case 13, the total white-cell count remained high and the liver, spleen, and lymph nodes showed only slight reduction in size. He developed severe thrombocytopenia (less than 50,000/c.mm.) resulting in fatal haemorrhage despite blood transfusions. Cases 14 and 15 had total doses of 700 mg. of mannomustine. Within three weeks one patient (Case 14) was in complete remission, which has continued for the past nine months, while the other gave only a partial remission, with a transient thrombocytopenia. No significant change in the haemoglobin from its initial normal level was noted in either patient.

Acute Leukaemia (6 Cases)

During the period of this trial we had available in our group of acute leukaemias six patients with high initial white-cell counts—three had acute monocytic leukaemia, one had acute myeloid leukaemia, one an acute lymphoblastic termination of an aplastic anaemia, and one an acute erythroid myelosis.

To each of these patients mannomustine was given in single doses of 100 mg. on alternate days for two to five doses in order to reduce the total white-cell counts to

TABLE II.—*Effect of Mannomustine in Acute Leukaemia*

Case No.	Age and Sex	Type	Before Treatment		Total Dose (mg.) 1st Course	After 1st Course		Days after Treatment	Duration of Response to 1st Course (Months)
			W.B.C. 10^9 /c.mm.	% Primitive Cells		W.B.C. 10^9 /c.mm.	% Primitive Cells		
16	40 M	Monocytic	54.5	88.5	400	9.5	76.5	14	2
17	49 M	"	116.0	93.0	450	9.1	81.0	10	2
18	67 F	"	64.0	34.5	200	8.2	28.5	5	(died)
19	52 M	Lymphoblastic	91.0	92.0	200	29.4	53.0	9	2
20	35 M	Myeloid	160.0	73.0	500	29.4	28.5	11	1
21	22 F	Erythromyelosis	102.0	74.0	200	31.0	64.5	11	1

TABLE III.—*Effect of Mannomustine in Hodgkin's Disease*

Case No.	Age and Sex	Total Dose mg. (mg./kg.)	Before Treatment				After Treatment				Duration of Response (Months)
			Clinical Condition	Hb g./100 ml.	W.B.C. 10^9 /c.mm.	Plts. 10^9 /c.mm.	Clinical Condition	Hb g./100 ml.	W.B.C. 10^9 /c.mm.	Plts. 10^9 /c.mm.	
22	48 M	700 (12.1)	Good P.G.++	14.5	8.8	103	Good P.G. 0	14.5	6.1	202	8*
23	14 M	1st course: 900 (20.7)	Fair P.G.+++ M.G.+++	11.1	5.8	236	Fair P.G. 0 M.G. 0	6.7	0.8	40	3
		12 wks. later: 600 (13.8)	Fair P.G.+++ M.G.+++ S+	7.4	2.2	145	Fair P.G. 0 M.G. 0 S 0	†	1.1	52	3*
24	76 F	700 (16.4)	Fair P.G.+ S++++ L++++	11.3	10.2	145	Good P.G. 0 S 0 L+	12.0	4.5	164	5*
25	32 M	900 (15.5)	Good Pruritus+++ P.G.++	14.0	7.5	256	Good Pruritus 0 P.G. 0	13.3	3.7	73	4*
26	28 F	1st course: 1,000 (15.9)	Fair Pruritus++ M.G.+++ Collapsed L.L. lobe	13.9	10.4	317	Good Pruritus 0 M.G. 0 L.L. lobe re-expanded	10.2	0.8	40	3½
		14 wks. later: 650	Fair M.G.+++ L. pleural effusion	13.3	8.9	205	Good M.G.+++ Effusion aspirated	11.2	3.5	37	2*
27	28 F	1st course: 700 (12.7)	Fair Pyrexial P.G.+++	12.7	7.5	210	Good P.G.+ Afebrile	9.7	2.8	148	1½
		7 wks. later: 300 (5.4)	Fair P.G.+++	10.2	4.7	175	Good P.G.+++	10.5	2.8	176	1
28	61 M	1,050 (14.5)	Good P.G.+++	14.2	4.2	157	Good P.G.+++	11.5	5.0	100	4
29	53 M	1st course: 900 (15.0)	Good P.G.++ S+	14.6	5.3	215	Good P.G.+ S 0	10.8	4.8	215	2½
		11 wks. later: 600 (10.0)	Good P.G.++	11.8	4.6	192	Good P.G.++	10.8	5.1	148	5
30	60 M	1,000 (14.3)	Poor P.G.++	8.9	8.4	222	Poor P.G.++	†	2.8	39	1½
31	26 M	700 (11.7)	Fair Pyrexia P.G.+ M.G.++	12.1	21.0	340	Good Afebrile P.G. 0 M.G.++	10.4	9.4	86	3*

P.G.=Peripheral glands. M.G.=Mediastinal glands. S=Size of spleen. L=Size of liver. * Continuing. † Given blood transfusions.

relatively normal levels and therefore facilitate the subsequent action of prednisolone and blood transfusions. This was achieved in all six patients (Table II). In Cases 16, 18, 20, and 21 subsequent relapses with rising total white-cell counts responded to further short courses of mannomustine. The remaining two patients died in acute relapse before further courses could be effective. Five of the patients improved with the combined therapy, in Case 16 complete regression of skin nodules, splenomegaly, and lymphadenopathy being obtained. One patient with acute lymphoblastic leukaemia died 11 days after the beginning of mannomustine injections. In none of the patients was complete remission obtained.

Reticuloses (14 cases)

Hodgkin's Disease

Ten patients with Hodgkin's disease were treated with mannomustine (see Table III). Two (Cases 28 and 29) had previously been treated with "thiotepa" and/or tri-(β -chloroethyl)amine hydrochloride ("trillekamin") with satisfactory remissions of two years and 15 months respectively. The initial total doses of mannomustine given have varied between 700 and 1,050 mg., according to the severity of the disease. Complete regressions of lymphadenopathy and/or splenomegaly were obtained in five patients and partial regressions in the remainder, in two of whom the responses were very poor. The duration of responses to the first course varied from six weeks to eight months, and second courses were given to four patients, the lymphadenopathy again showing regression in two of them.

After being maintained for six to seven weeks the haemoglobin levels fell suddenly in six patients (Cases 23, 26, 27, 28, 29, and 31), but subsequently showed improvement within three weeks. Neutropenia was noted in five patients (Cases 23, 25, 26, 27, and 30) after five to six weeks, and in Cases 23 and 26 it was severe, the total white cells being below 1,000/c.mm. Thrombocytopenia, maximal after four to five weeks, occurred in five patients; it was symptomless and transient in four (Cases 23, 25, 26, and 31), while in one (Case 30), who was in the terminal stage of the disease, the thrombocytopenia had persisted for the seven weeks before he died. The value of mannomustine in the management of Hodgkin's disease is illustrated in the following examples of cases responding to treatment.

Case 22.—A 48-year-old man presented with enlarged cervical and axillary glands. Biopsy showed typical Hodgkin's disease. He was given mannomustine, 100 mg. daily, to a total of 700 mg. Complete regression of the glands occurred within three weeks. The blood picture remained normal. There has been no recurrence over eight months.

Case 23.—A 14-year-old boy had enlarged cervical and mediastinal glands. Biopsy showed Hodgkin's disease. He was given mannomustine, 300 mg. daily, to a total of 900 mg. All glands had completely regressed in two weeks. Within four weeks he had developed a pancytopenia with agranulocytosis and was given prednisolone, 30 mg. daily, for three weeks. The white blood cells and platelet counts returned to normal levels within two weeks, the red blood cell count and haemoglobin responding more slowly. He relapsed within three months, and a second course of mannomustine, 100 mg. on alternate days, to a total of 600 mg. was given. Complete regression of all glands again occurred within two weeks and continued to the time of writing (three months). He developed an aplastic anaemia which has failed to improve with prednisolone, but he was being maintained satisfactorily by transfusions.

Case 24.—A 76-year-old woman had gross enlargement of the liver and spleen and enlarged cervical glands. Biopsy showed Hodgkin's disease. She was given 100 mg. of mannomustine daily to a total of 700 mg. Complete regression of the spleen and marked reduction in hepatomegaly occurred in six weeks; the blood count remained normal, but four months later the spleen was again just palpable.

Brill-Symmers Disease

Two patients with follicular lymphoreticulosis were treated with mannomustine. One with gross hepatomegaly and obstructive jaundice was given single injections of 500 mg. on alternate days to a total of 1,000 mg. Rapid regression of the hepatomegaly, and relief of the obstructive jaundice occurred within 10 days, the only toxic effect being a transient thrombocytopenia. She relapsed two months later and died. The second patient was confined to bed with severe lumbar pain due to spinal-nerve-root compression. He was given a total of 800 mg. of mannomustine in 100-mg. daily doses. Complete relief of all symptoms and signs of compression occurred within four weeks, and he has been fully ambulant and working for the past four months. He showed a mild transient anaemia and thrombocytopenia.

Reticulosarcoma

Mannomustine has been given to two patients with reticulosarcoma. In a man aged 57, who received two courses of mannomustine to a total of 1,000 mg. and 1,750 mg. respectively, the only beneficial effect noted was a temporary regression of the glands and extensive secondary skin nodules following the second course of mannomustine, but the massive total chemotherapeutic treatment given, which had also included trillekamin, failed to halt progression of the disease, and resulted in the production of a profound aplastic anaemia after 21 weeks, with death eight weeks later. Complete regression of the marked cervical lymphadenopathy was obtained in the second patient, a man aged 50, who was given mannomustine to a total of 700 mg. in the first course, the remission lasting only nine weeks; the glands have again regressed following treatment with a further 700 mg. A transient thrombocytopenia occurred after both courses of treatment.

Multiple Myeloma (1 case)

Complete relief of bone pain, regression of hepatomegaly and splenomegaly, a slight fall of the raised serum globulin level, and a fall to normal of the sedimentation rate have occurred after a total dose of 1,000 mg. of mannomustine given to one patient. The x-ray appearances of numerous skeletal deposits have not changed, but the marked symptomatic improvement has been maintained for three months.

Carcinoma (5 Cases)

Five patients suffering from advanced carcinoma have been given mannomustine. The total dose has ranged from 700 to 1,100 mg. Three patients had bronchial carcinoma with multiple secondary deposits, one patient had carcinoma of the stomach with secondary deposits in the liver, and one had a carcinoma of the breast with multiple secondaries elsewhere.

In one patient with a malignant pleural effusion, the mannomustine was given intrapleurally, as much as 500 mg. being injected at one time, without any immediate local or general adverse effects.

Beneficial effects were slight; temporary regression of secondary deposits in lymph nodes was noted in two patients, and relief of pain for a period of three weeks was obtained in two others, but there was no effect on the primary growth or on any liver or secondary skin deposits. Anaemia developed in all patients within six weeks; a severe neutropenia occurred in two patients and thrombocytopenia in two others, resulting in death from gastro-intestinal haemorrhage in one of them.

All five patients died within eight weeks of beginning treatment with mannomustine.

Polycythaemia (4 cases)

The effect of treatment with mannomustine in four cases of polycythaemia is shown in Table IV. The mannomustine was given in doses of 100 mg. on alternate days until the total amount had been given.

Beneficial effects were obtained in all the patients, and in three of them (Cases 32, 34, and 35) the remissions were continuing after six, four, and three months respectively. Case 33 required a further short course of mannomustine after six weeks. One patient (Case 32) suffered from severe pruritus, which had failed to respond to all previous treatments, but complete relief of this symptom followed mannomustine therapy. The spleen was enlarged in Cases 34 and 35 and became impalpable after treatment. A transient leucopenia occurred in two patients after six weeks, and there was a symptomless transient thrombocytopenia in three patients after three to five weeks.

Toxic Reactions

Gastro-intestinal.—Of the 45 patients treated with mannomustine, 19 (42.2%) had some gastro-intestinal side-effects—*anorexia, nausea, or vomiting*. At some time during the course of treatment 41 patients were given individual doses of 100 mg. (1.5–2.5 mg./kg.): mild *anorexia* and *nausea* occurred in 13 (31.7%) and *vomiting* in 6 (14.6%). Doses greater than 100 mg. were usually associated with severe *nausea* and *vomiting*. In 17 patients individual doses of 150–500 mg. were given. Of these, 5 (29.4%) had no gastro-intestinal side-effects, one patient receiving two injections of 500 mg. each on alternate days. *Nausea* and *malaise* began three to six hours after the injection and lasted for between 4 and 36 hours. When patients were treated on alternate days they had normally recovered before the next injection. Rarely, toxic symptoms would last for two to three days. In those patients who complained of *nausea* and *vomiting*, a decrease in symptoms following the use of 1,000 mg. of ascorbic acid in aqueous solution as a solvent, in place of physiological saline, was noted in some patients, and the simultaneous use of chlorpromazine (25 mg. four times daily) often resulted in further reduction or relief of symptoms. Intrapleural injections of 50–500 mg. have been given without ill effects.

Local Reactions.—In three patients a small volume of the mannomustine solution accidentally leaked into the

extravascular tissues. The patients complained of severe pain at the injection site within three to four hours, and each developed an extremely tender, erythematous, indurated mass which slowly enlarged over a period of two to three weeks. The mass was still present four to five months later.

Bone Marrow.—Table V shows the frequency with which the severe but mostly transient depression of bone-marrow function occurred after mannomustine

TABLE V.—Toxic Effects on Bone Marrow Following Treatment With Mannomustine (Excluding Acute Leukaemias)

Diagnosis	No. of Patients	Anaemia	Leucopenia	Thrombocytopenia
Chronic myeloid leukaemia	12	—	1	1
"lymphatic "	3	—	—	1
Hodgkin's disease	10	6	5	5
Brill-Symmers disease	2	1	1	1
Reticulosarcoma	2	1	1	2
Myeloma	1	—	1	1
Carcinoma	5	5	2	2
Polycythaemia	4	—	2	3
Total	39	13 (33%)	13 (33%)	16 (41%)

therapy. The thrombocytopenia developed within four to five weeks and leucopenia within five to six weeks after the beginning of treatment; both were usually symptomless and lasted two to three weeks only. Granulocytes and lymphocytes were depressed equally in most cases, only one patient developing a temporary agranulocytosis. Two patients with Hodgkin's disease (Cases 23 and 26) who were each given a second course of mannomustine three months and four months later, respectively, again developed marrow depression, which has lasted two to three months and has failed to improve with steroid therapy. Anaemia, developing six to eight weeks after treatment, was particularly frequent in the patients with reticulosos or malignant disease. In the patients with a reticulosis, the haemoglobin had usually returned to near pre-treatment level within six weeks, but two developed persistent aplastic anaemia after the second course of treatment. In four patients the principal cause of death was aplastic anaemia or haemorrhage from thrombocytopenia. They were, however, in the terminal stage of their illness. Prednisolone did not appear to facilitate marrow recovery.

Discussion

In this series of cases the percentage with gastro-intestinal side-effects (42.2%) after doses of 1.5 to 2 mg./kg. was similar to that reported by Sellei and Eckhardt (1958). When doses of 3 to 7 mg./kg. were given the percentage increased considerably (70.6%). Like Szentkláray (1958), we observed some reduction of these side-effects when the drug was dissolved in ascorbic acid solution instead of physiological saline. Concurrent administration of chlorpromazine was of value in some patients. Sellei and Eckhardt, from the results in their series of cases treated with mannomustine over a period of two years, consider the drug to be superior to other chemotherapeutic agents in chronic lymphocytic

TABLE IV.—Effect of Mannomustine in Polycythaemia Vera

Case No.	Age and Sex	Before Treatment					Total Dose mg. (mg./kg.)	After Treatment					Duration of Response (Months)
		R.B.C. $10^9/c.mm.$	Hb g./100 ml.	P.C.V. %	W.B.C. $10^9/c.mm.$	Plts. $10^9/c.mm.$		R.B.C. $10^9/c.mm.$	Hb g./100 ml.	P.C.V. %	W.B.C. $10^9/c.mm.$	Plts. $10^9/c.mm.$	
32	75 F	6.73	16.4	—	34	545	800 (18.2)	4.22	11.1	—	2.3	51	6
33	54 M	6.32	13.0	—	5.1	204	500 (5.5)	5.9	10.5	—	No change	No change	1.5
34	64 M	16.6	—	72	25	562	800 (11.0)	5.4	15.5	35	5.4	37	4
35	47 M	8.72	23.6	76	10	270	900 (13.6)	5.6	17.0	47	2.4	51	3

leukaemia and equal to other drugs in chronic myeloid leukaemia. They stressed the value of combined treatment with mannomustine and busulphan or demecolcine in chronic myeloid leukaemia, but did not state in how many cases this combined therapy was used. They also reported favourable results in Hodgkin's disease, other reticuloses, and multiple myeloma.

Our results in chronic myeloid leukaemia were disappointing. A satisfactory response was obtained in only two patients, both of whom shortly relapsed. In the remaining 10 patients control was inadequate and of very short duration, apart from one patient with an extremely sensitive bone marrow, the white-cell count remaining under 25,000/c.mm. for over eight months. The responses to further courses of mannomustine given to six patients were even less satisfactory than those following the initial courses.

That mannomustine may be effective in cases resistant to other chemotherapeutic agents is illustrated by one patient (Case 11) who had become resistant to busulphan and failed to respond to intravenous nitrogen mustard (trillekamin). A satisfactory reduction in the white-cell count was achieved with mannomustine; it was unfortunately of short duration, and the patient refused further injections because of very severe nausea and vomiting.

Apart from the generally unsatisfactory response of chronic myeloid leukaemia to mannomustine therapy, the practical difficulties of administering daily or alternate daily intravenous injections to out-patients who may have to travel considerable distances to attend the clinic makes the drug very much inferior to busulphan, which is undoubtedly the drug of choice (Galton and Till, 1955; Wilkinson, 1955a, 1955b).

Although three is too small a number of cases to assess adequately the value of a drug, our patients with chronic lymphocytic leukaemia have illustrated the considerable variation in response that can be obtained. The responses in further patients treated with mannomustine will have to be very much better if the drug is to compare favourably with trillekamin (Wilkinson, 1953, 1955a, 1955b) or chlorambucil (Galton *et al.*, 1955).

Mannomustine would appear to be of some value in Hodgkin's disease, good responses being obtained with five patients and moderately good ones with four others. The responses, however, were not as good as have been achieved with trillekamin; many more injections were required, and they produced more toxic effects generally and on the bone marrow than are obtained with trillekamin (Wilkinson, 1955a, 1955b). Mannomustine would appear to be more effective than thiotepe in Hodgkin's disease, as complete regressions of hepatomegaly, splenomegaly, and mediastinal lymphadenopathy have been obtained in most cases, whereas thiotepe is relatively inactive in Hodgkin's disease involving these structures (Leonard *et al.*, 1956). Toxic effects on the bone marrow, however, were much more marked than with thiotepe.

Two cases of Brill-Symmers disease and one of reticulosarcoma benefited from treatment, and the patient with multiple myeloma showed such good symptomatic and some objective improvement that it will be worth while treating further cases either with mannomustine alone or in combination with urethane. Mannomustine was of little value in the five cases of carcinoma: indeed, the severe anaemia and the thrombocytopenia produced in two cases may well have

contributed in some degree to their more rapid deterioration.

Satisfactory remissions have been obtained in three patients with polycythaemia vera, while the fourth patient, who was initially given a small total dose, is now responding satisfactorily to a second course of mannomustine. It is not yet known whether remissions of comparable length to those obtained using other agents such as thiotepe (Leonard *et al.*, 1956) will occur, but mannomustine may prove to be another useful method of treatment.

In addition to the reduction of the occasionally observed high white-cell count in some acute leukaemias, the simultaneous symptomatic improvement that was also obtained would appear to support the careful use of mannomustine in such types of case.

Disadvantages of mannomustine treatment in diseases other than chronic myeloid leukaemia are (a) the potentially serious although usually transient bone-marrow depression, especially if a second course is given within four months of the first; (b) in many cases there may be undesirable gastro-intestinal side-effects; and (c) occasional painful local effects.

This bone-marrow depression does not appear to respond to prednisolone.

Summary

A new cytostatic compound mannomustine (1:6-bis(β -chloroethylamino) - 1:6 - deoxy - D - mannitol dihydrochloride) has been used in the treatment of 45 patients with leukaemias, polycythaemia, reticulosis, and malignant disease.

A dosage schedule of 100 mg. daily or on alternate days to the required total amount is the most satisfactory.

It was not found to be as efficient as the present accepted agents such as trillekamin, busulphan, or demecolcine for the treatment of chronic myeloid leukaemia.

Mannomustine is of some value in the treatment of chronic lymphatic leukaemia, Hodgkin's disease, Brill-Symmers disease, reticulosarcoma, multiple myeloma, and polycythaemia.

Pain may be relieved in carcinoma, but severe bone-marrow depression may occur.

Mannomustine may be of value in the treatment of acute leukaemia, particularly the monocytic type, if the initial white-cell count is much increased.

Toxic effects can be severe, particularly on the bone marrow and especially if a second course has been given within four months; gastro-intestinal side-effects, nausea, or vomiting occur in 42% of patients after single doses of 1.5-2 mg./kg., but as high as 70% after doses of 3-7 mg./kg.

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