Papers and Originals**TREATMENT OF LEUKAEMIAS AND RETICULOSES
WITH URACIL MUSTARD**

BY

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It is 25 years since one of us (Wilkinson and Fletcher, 1947) began to use the nitrogen mustards, tri-(2-chlorethyl)amine hydrochloride ($\text{Cl.CH}_2\text{CH}_2)_3\text{N HCl}$ and methyl-di-(2-chlorethyl)amine hydrochloride, $\text{CH}_3(\text{Cl.CH}_2\text{CH}_2)_2\text{N HCl}$, intravenously in the treatment of chronic myeloid and lymphatic leukaemias, Hodgkin's disease, and reticuloses generally. The former substance proved to be, and still is, the most effective and most easily controlled general treatment for these conditions, but it tends in some cases to cause nausea and vomiting. Nevertheless the rapidity and efficiency with which it reduces grossly enlarged spleen, liver, and lymph nodes, and in many cases the subsequent prolonged clinical effects, make it a very desirable therapeutic agent. In the past 18 years many other chemotherapeutic agents have been produced, particularly with the object of finding an equally efficient preparation that could be given orally. Clinical trials have shown some of these to have value in the treatment of one group or other, but none have really had the same almost universal clinical value and efficiency for all these groups of chronic leukaemias and reticuloses.

More recently, however, Lyttle and Petering (1958), by introducing the uracil grouping into the molecule of tri-(2-chlorethyl)amine, synthesized 5-di-(2-chlorethyl)-aminouracil (uracil mustard, or U8344), a substance that could be given orally to patients, producing results almost identical to those obtained with intravenously administered tri-(2-chlorethyl)amine hydrochloride in chronic myeloid and lymphatic leukaemias, Hodgkin's disease, and the reticuloses. Uracil mustard is a white crystalline substance that can be given orally with minimal toxic side-effects. It was shown by Evans and Mengel (1958), Lyttle and Petering (1959), and Lane and Kelly (1960) to be active against various tumours in small animals, and its anti-tumour effects against malignant disease were reported by Lane and Kelly (1959a, 1959b), by Lane *et al.* (1960), and by Vaitkevicius *et al.* (1961).

Shanbrom *et al.* (1960) reported satisfactory responses with this uracil mustard in their clinical trials on patients with lymphomas and ovarian carcinoma.

Since 1959 generous quantities of this uracil mustard have been made available to us for clinical trial by

Messrs. Upjohn Ltd. through Dr. R. G. Jacomb, and we have been able to carry out a trial of its value in the treatment of chronic myeloid and lymphatic leukaemias, Hodgkin's disease and other reticuloses, lymphomata, and malignant diseases.

This is a brief preliminary report of a four-year trial.

Dosage and Control

Uracil mustard has been given orally to our patients, usually beginning with an initial dose of 3–5 mg. daily orally either in single or in divided doses after meals, the dose being reduced to 1–3 mg. daily and subsequently to 1 mg. once or twice weekly, according to the clinical and haematological responses of the patients, many of whom were treated as out-patients, admission to hospital being unnecessary for them for this purpose.

In general, uracil mustard in our experience has been singularly free from toxic or undesirable side-effects on this dosage scheme, but the occasional patient may have slight gastro-intestinal disturbances, which clear up promptly with a diminution in the dosage.

Chronic Myeloid Leukaemia

Twenty-one patients (13 males, 8 females) with chronic myeloid leukaemia have been given uracil mustard orally; their ages varied from 19 to 72 when first seen, and they had been known to have had the disease for periods of up to five years. Three of them had been treated previously with busulphan or intravenous trimustine hydrochloride ("trillekamin"); and one had pernicious anaemia, one diabetes mellitus, while a third became pregnant during treatment, the foetus being stillborn, as usually occurs in leukaemia. The uracil mustard was initially given to these patients in a dosage of 3–5 mg. daily, and then the dose was adjusted according to the blood count and clinical responses. One patient had 10 mg. daily without any untoward effects.

The spleen was much enlarged in all 21 patients, but this treatment with uracil mustard greatly reduced it in size in 19 of them, and it became impalpable in five; in only two did it remain unchanged. The livers were enlarged in 17—greatly so in seven—but they returned to normal after treatment in all except one. Nine patients had enlarged lymph nodes, and in all cases these became impalpable.

The peripheral white-cell count was considerably raised in all at the beginning of treatment. Only two had white-cell counts below 100,000/c.mm., eight lay between 100,000 and 200,000, and 11 were greater than 200,000—the highest being 501,000. The white-cell counts were reduced in all to the desired level of 15,000–20,000, except in one patient. In 19 of the 21 patients the white-cell count was reduced to half within two weeks of receiving the uracil mustard and eventually to

less than 20,000 in 20 of them. Of the three patients whose platelet counts were less than 100,000 when first seen, two died within 12 weeks and in one the platelet count rose on treatment, though the patient showed only a little improvement. While the patients were on the uracil mustard the platelet counts fell below 20,000 in five, all of whom died within four months—two from cerebellar haemorrhages and one with a subdural haematoma.

Of the 21 patients treated with uracil mustard in the four-year trial, nine have lived 18 months, five for three years, and one for three and a half and four years, respectively (Table I).

TABLE I.—*Chronic Myeloid Leukaemia (21 Patients—13 Males Aged 28–72, 8 Females Aged 19–71)*

	Before Treatment	After Treatment
Enlarged spleen	21	2
„ liver	17	1
„ glands	9	0
White-cell count/c.mm.: < 100,000	2	20 < 20,000
100,000–200,000	8	
200,000–500,000	11	

Case Report

A 47-year-old housewife had noticed that she had been pale and had lost weight for about one year. The liver was enlarged to about 1 in. (2.5 cm.) below the right costal margin and the spleen was level with the umbilicus. Her blood count on admission was: Hb 9.4 g./100 ml., white cells 321,000/c.mm. (polymorphonuclears 45%, lymphocytes 1%, monocytes 2.5%, eosinophils 1%, basophils 3.5%, metamyelocytes 24.5%, myelocytes 15.5%, megakaryocytes 0.5%, promyelocytes 4.5%, blasts 2%), platelets 860,000/c.mm. The sternal marrow was typical of chronic myeloid leukaemia. She was given uracil mustard 5 mg./day orally, and after seven days the dose was reduced to 5 mg. on alternate days as the white-cell count had fallen to 68,500; after a further four days' treatment it was stopped, the count then being Hb 10 g., white cells 24,100, and eight days later the haemoglobin was 11.8 and white-cell count 6,400. Two weeks after discharge from hospital she felt very well; her spleen could only just be felt and the liver was impalpable.

Five weeks later the spleen had enlarged to 2 in. (5 cm.) below the costal margin and the white-cell count had risen to 57,000; a further course of 2 mg. of uracil mustard daily was therefore given for three weeks, when the white-cell count again fell to 8,100. No treatment was given for the next four weeks, when the white-cell count rose to 22,000; then 1 mg. of uracil mustard was given on alternate days for a month until the white-cell count had fallen to 12,200. There was no treatment for the next four months, the white-cell count remaining about 15,000, while the spleen could barely be felt and she was very well. The white-cell count gradually rose to 28,000, so 1 mg. of uracil mustard was given twice weekly. For the next 18 months she took 1 to 3 mg. of uracil mustard weekly, depending on the white-cell count, which was usually between 15,000 and 30,000, with a haemoglobin level between 11.7 and 13.1 g./100 ml. She had felt very well throughout this time, and only at the end of this period had the spleen again become very slightly enlarged. It is now some three years since treatment with uracil mustard was begun.

Chronic Lymphatic Leukaemia

Eighteen patients (11 males, 7 females) with chronic lymphatic leukaemia were treated with uracil mustard: their ages varied from 47 to 81. They had had symptoms for up to two years prior to treatment with uracil mustard. One patient had pernicious anaemia, one had previously been given chlorambucil and prednisolone, one had had thiotepea, and another had received these

three drugs as well as tretamine, mannomustine, nitrogen mustard, and x-ray therapy. Uracil mustard was given orally to these patients in doses of 2–5 mg. daily as described above.

Sixteen of the patients had much enlarged peripheral glands, which, after uracil mustard, diminished considerably in size in 13. Fourteen patients had enlarged spleens, eight of which were much reduced in size; in 11 the liver was enlarged, and in five of these the size was reduced very much after treatment (Table II).

TABLE II.—*Chronic Lymphatic Leukaemia (18 Patients—11 Males Aged 47–76, 7 Females Aged 55–81)*

	Before Treatment	After Treatment
Enlarged spleen	14	6
„ liver	11	6
„ glands	16	3
White-cell count/c.mm.: 50,000	1	13 < 20,000
50,000–100,000	7	
100,000–200,000	4	
200,000–500,000	6	

The initial white-cell counts were raised in all the patients except one who had had previous treatment; seven had white-cell counts of 50,000–100,000, four of 100,000–200,000, and six of 200,000–500,000. The white-cell count was reduced in all the 17 patients with a raised initial count; in 14 it was reduced to half within two weeks, while in 13 it fell below 20,000 eventually. The platelet counts fell below 20,000 in seven patients at some time during the courses of treatment, but in only two of these was any bruising observed. Nine patients have died since treatment was begun (one from an accident)—four within nine weeks of beginning treatment, one of congestive heart failure, and one with a lung abscess. One patient vomited on several occasions when given uracil mustard. Of these 18 patients, six have had treatment for more than two and a half years and are alive and well; others have had shorter periods of treatment.

Case Report

A 56-year-old farmer was first seen in January, 1960. For a few weeks he had noticed that he was losing energy and weight, and he had had a few nasal epistaxes. Small lymph nodes were present in his neck, groins, and axillae. His spleen was palpable 2 in. (5 cm.) below the left costal margin. The blood count was: Hb 12.9 g./100 ml., white cells 60,000/c.mm. (of which 62% were lymphocytes), and platelets 102,000/c.mm. The sternal marrow was characteristic of chronic lymphatic leukaemia. Uracil mustard (5 mg.) was given on alternate days; after two weeks he felt much better, though he had slight nausea from the drug. His spleen was barely palpable and only one lymph node could be felt in his left axilla. The white-cell count had fallen to 15,850 and the uracil mustard was reduced to 5 mg. weekly for the next two weeks, and then increased to 5 mg. twice a week.

He was still having nausea about 12 hours after taking the 5-mg. capsules. The uracil mustard was reduced to 2 mg. on alternate days and he had no further nausea. After two weeks the dose was further reduced to 1 mg. on alternate days for three weeks only. The white-cell count was 8,300, but after four months without treatment it again rose to 32,800. Uracil mustard (1 mg. on alternate days) was given for four weeks and the white-cell count fell to 15,650, the dose then being reduced to 1 mg. weekly. When the treatment was stopped the lymph nodes in his neck began to enlarge again, the white-cell count being 10,500, so uracil mustard (1 mg.) was given on alternate days and then on every third day for the next four months; during this time his lymph nodes were very small. The white-cell count later rose to 29,000, so the dose was increased to 1 mg.

daily for two weeks, leading to a fall to 14,000. For six months 3 mg. of uracil mustard was continued weekly and the white-cell count remained about 16,000. After this the dose was reduced to 2 mg. weekly for three months and then to 1 mg. weekly. No lymph nodes could be palpated, nor was the spleen enlarged. The white-cell count varied between 7,400 and 11,200 on this dose. He continued very fit and well after a total period of 37 months, and had taken 1 mg. three times weekly for the last six months.

Acute Leukaemia

Uracil mustard has been given to four patients with acute myeloblastic leukaemia who had high white-cell counts (55,000–176,000) and consequently were very ill when the treatment was begun.

All four patients were already on treatment with prednisolone and blood transfusions. After uracil mustard was given the white-cell counts fell at first very rapidly, and two of the three patients who received a second course later showed similar responses. There was little diminution in the size of the enlarged lymph nodes, tonsils, liver, or spleen in any of these patients. One patient felt much better after his first course of treatment, but he quickly relapsed and his white-cell count rose again, while the platelets fell during a second course of uracil mustard. Another patient, who had ovarian cysts, showed a similar fall in white-cell count, but she remained very ill, dying 13 days later of pneumonia. Although the white-cell count in a further patient was reduced after uracil mustard there was no improvement in her clinical condition.

Case Reports

1. A 55-year-old housewife had a two-months history of anorexia, lassitude, and loss of weight. She also complained of a sore throat. A few small lymph nodes were felt in her left axilla and neck, and she had bruises on her legs. The liver and spleen were not palpable. Her initial blood count was: Hb 12.9 g./100 ml., white-cell count 50,000/c.mm. (blasts 68%), and platelets 104,000/c.mm. The sternal marrow confirmed the diagnosis of acute myeloblastic leukaemia, the marrow being very cellular, with large numbers of myeloblasts and stem-cells with prominent nuclei; there were frequent mitoses. Prednisolone 100 mg./day and uracil mustard 3 mg./day were given. On the first day the white-cell count was 60,500 and after two, four, and five days the white cells numbered 49,400, 18,200, and 10,100 respectively, while the platelets fell to 70,000. The uracil mustard was stopped after six days, when the white-cell count was 7,400. Ten days later it was 600 and the platelet count 130,000. Sixteen days later her Hb was 12.9 g./100 ml., white cell count 176,000 (blasts 66.5%), and platelets 68,000. By now she was on prednisolone 25 mg. daily. Uracil mustard 2 mg. daily was given for two weeks, at which time she had many ecchymoses, as usual, and the prednisolone dosage was increased to 50 mg. daily by mouth. A week later she felt fairly well, though she still had the ecchymoses. Her Hb was 10.8 g./100 ml., white-cell count 56,000 (blasts 78%), and platelets 15,000. At this stage 6-mercaptopurine was given, which led to rapid deterioration, and she died 11 weeks later. Necropsy showed widespread purpuric haemorrhages and acute heart failure with pulmonary oedema.

2. A 16-year-old boy with acute lymphatic leukaemia was treated with uracil mustard. He had had gross swelling of the cervical and inguinal lymph nodes for four months, an enlarged spleen palpable about 4 in. (10 cm.) below the costal margin, and a dusky-red rash on his abdomen and back. He had already had courses of intravenous trimustine and prednisolone. The blood findings were: Hb 10.5 g., white cells 32,000 (polymorphs 24%, lymphocytes 48.5%, monocytes 1.5%, blasts 26%), and platelets 11,000. He was

given uracil mustard 5 mg. daily for 10 days and after four days his lymph nodes were much reduced in size and softer, and he felt much better. The count was: Hb 10.2 g., white cells 2,900 (polymorphs 46%, lymphocytes 43.5%, monocytes 1%, eosinophils 1%, basophils 0.5%, blasts 8.5%), and platelets 10,000. Although the uracil mustard had reduced the peripheral white-cell count and the size of his lymph nodes, the latter became enlarged again later when treatment was discontinued.

3. A housewife aged 70, with acute reticulum-cell leukaemia, was given uracil mustard. Her liver and spleen were palpable about 4 in. (10 cm.) below the costal margin and she was in congestive cardiac failure. The initial blood count was: Hb 5 g., white cells 26,000 (of which 32% were blasts, mostly of a primitive reticulum-cell type), and platelets 28,000. The sternal marrow confirmed the diagnosis of acute reticulum-cell leukaemia. The white-cell count rose to 85,000 and she was given uracil mustard 5 mg. daily; blood transfusions were also given because of the anaemia. After seven days the white cells had fallen to 6,900 and the uracil mustard was stopped two days later. The white-cell count continued to fall, reaching 500 seven days later. Her general condition had been deteriorating during this time and she had melaena, haemoptysis, epistaxes, and purpura, while the haemoglobin fell despite further blood transfusions, prednisolone, and phenbenicillin potassium salt ("penspek"). She died one week later.

Polycythaemia Vera

Five patients with polycythaemia were treated with uracil mustard. All had previously been treated by venesections and thiotepea (Leonard *et al.*, 1956), while one had received intravenous trimustine and one busulphan. Three patients showed little or no response other than some fall in the platelet count, while one took his tablets very irregularly and showed no response to this form of treatment. All have responded to other forms of treatment. One patient showed some improvement.

Case Report

A 59-year-old company director had had polycythaemia for four years and also had gout. After six weeks' treatment with 2 mg. of uracil mustard daily the red cells had fallen from 7,000,000 to 4,574,000/c.mm., the white cells from 29,000 to 8,150/c.mm., and the platelets from 219,000 to 38,000/c.mm. Eight weeks after withdrawal of the uracil mustard the platelets had risen to 351,000. At this time the Hb was 11.5 g., red cells 6,246,000, and white cells 10,900. Treatment was recommenced and after a further three-weeks course of 2 mg./day the Hb was 12.3 g., red cells 6,061,000; white cells 8,600, and platelets 174,000. Ten months later 98 mg. of uracil mustard was given over six weeks (in a dosage of 2–3 mg./day). Initially the Hb was 10.6 g., red-cell count 7,247,000, white-cell count 19,600, platelets 380,000; at the end of the course Hb was 10.6 g., red-cell count 6,696,000, white-cell count 9,000, and platelets 85,000. One week later the platelet count was 64,000, though it rose later.

Hodgkin's Disease

Twenty-eight patients (18 males, 10 females) with Hodgkin's disease have been treated with uracil mustard; their ages ranged from 16 to 59 at the beginning of treatment. Some were known to have had the disease for up to 13 years. Many had previously

TABLE III.—Hodgkin's Disease (28 Patients—18 Males Aged 16–59, 10 Females Aged 17–56)

	Before Treatment	After Treatment
Generalized enlarged lymph nodes	24	7
Enlarged spleen	4	2
Deposits in chest wall	1	0
„ „ jaw	1	0

received other nitrogen mustards, chlorambucil, thiotepa, prednisolone, A.C.T.H., mannomustine, and radiotherapy. One patient developed tuberculosis while on treatment. The dosage of uracil mustard usually given was 1-2 mg. daily, but sometimes up to 5 mg. daily was used, some patients having had 1-2 mg. weekly for more than three years.

Twenty-four patients had enlarged peripheral lymph nodes; in 17 of them uracil mustard reduced these nodes greatly in size, while in two the size was increased; 5 of the 24 had enlarged nodes in the neck only; three of these showed very marked reduction after treatment. Enlarged mediastinal nodes were present in eight patients, but in only one did they definitely diminish in size radiologically while on uracil mustard. The spleen was much enlarged in four patients, and in two of them the splenomegaly disappeared completely on treatment. Lymphadenomatous deposits in the chest wall were considerably reduced in size in one patient, and in the jaw in one.

The platelet counts fell to below 76,000 in 17 patients and to 15,000 or less in three, but in only one was there any purpura. The white-cell count fell to below 4,000 in 14 patients and to below 2,000 in three. Four complained of nausea while on the drug and three had vomiting. Diarrhoea occurred in two patients, while one had abdominal pain and vomiting. One patient vomited when given 5 mg. of uracil mustard daily but did not do so on 1 mg. daily.

Case Report

A county surveyor aged 34 had had a recurrent sore throat for some years. In 1955 he noticed enlarged nodes in his neck, but only non-specific changes were seen on subsequent biopsy and tonsillectomy. In November, 1956, he again noticed a mass of enlarged nodes in the left side of his neck extending under his left jaw and down to the left supraclavicular region. A lymph-node biopsy confirmed the diagnosis as Hodgkin's disease. On treatment with intravenous nitrogen mustard the enlarged nodes disappeared. After four months the enlarged nodes had reappeared in the left side of his neck and the administration of thiotepa intramuscularly resulted in no change in their size. After a further course of intravenous nitrogen mustard the glands regressed completely. Two months later they enlarged once more, and since chlorambucil had had little effect he was given further injections of intravenous nitrogen mustard, which again resulted in the disappearance of the nodes. After a further three months they became prominent once more but responded to intravenous nitrogen mustard. The left posterior auricular lymph nodes became enlarged five months later, failed to respond to chlorambucil, but improved again with intravenous nitrogen mustard.

In June, 1959 (three and a half years after his first course of treatment with nitrogen mustard), the lymph nodes reappeared in the left side of his neck, and this time he was given 2 mg. of uracil mustard daily, the Hb being 14.7 g. and white-cell count 7,800. After six weeks' treatment no lymph nodes could be palpated in his neck, and his haemoglobin was 13.3 g., white-cell count 3,400, and platelets 179,000. Six weeks later two very small nodes could be felt in the left side of his neck, but they did not change in size during the next 10 months.

In July, 1960, as the nodes appeared to be enlarging once more in size and increasing in number, he was given uracil mustard 1 mg. daily (Hb 12.9 g., white cells 5,200, and platelets 215,000); no lymph nodes could be palpated and he felt very well. Six months later a few small nodes had reappeared in the left side of his neck and uracil mustard was again given—1 mg. daily for a week, followed by 1 mg. on alternate days for a further three weeks, the lymph

nodes again disappearing. After a further three months without treatment an enlarged lymph node was noted in his right axilla. Uracil mustard was then restarted—1 mg. daily for two weeks and then 1 mg. on alternate days for six weeks—and the gland decreased in size. One month later the node had enlarged somewhat and uracil mustard was again given—1 mg. daily for one week and then 1 mg. on alternate days for a further week. After an interval of six weeks the uracil mustard was repeated similarly; as the axillary lymph node was still enlarged, though to a lesser degree, he was given 1 mg. on alternate days for two weeks and then 1 mg. weekly for the next four months.

He began to lose weight about this time and had some pain in the mid-dorsal region; there was one small lymph node in his right axilla, but x-ray examination also disclosed a large paraspinal soft-tissue mass extending from the level of vertebrae T5 to T7 on both sides, while an abnormal bone texture was noted in the bodies of T5, T6, and T7. The uracil mustard was increased to 2 mg. daily for the next week and then to 3 mg. daily for a week before being reduced to 1 mg. daily. A further chest x-ray film then showed considerable reduction in the size of the paraspinal shadows and no abnormality could be seen in the vertebrae themselves. The uracil mustard was continued in a dosage of 1 mg. daily. Throughout these last courses of treatment the white-cell count did not fall below normal levels nor did the platelet count fall below 100,000.

Brill-Symmers's Disease

Case Report

An estimating engineer aged 36 with Brill-Symmers's disease was treated with uracil mustard. He had noticed enlarged lymph nodes in his groin and later in his axillae and neck for nine months. For five months his abdomen had been swollen and he was becoming tired, dyspnoeic, and pale. Very large, firm lymph nodes were present in his groins, axillae, and neck, his spleen was enlarged 6 in. (15 cm.) below the left costal margin and his liver 3 in. (7.5 cm.) below the right costal margin. Bilateral pleural effusions were present and he had some sacral oedema. Biopsy of a lymph node confirmed the diagnosis of Brill-Symmers's disease. He was given chlorothiazide, and 2½ pints (1.4 litres) of fluid were removed from his right pleural cavity by aspiration. A blood examination when he was put on uracil mustard showed Hb 13.6 g., white cells 7,400, platelets 185,000.

He was given 3 mg. daily for two weeks, and at the end of this time the Hb was 13.3 g., white cells 5,100, and platelets 180,000, and his lymph nodes had diminished in size.

Four weeks later, after the uracil mustard had been discontinued, a chest x-ray examination showed the pleural effusions to have cleared, no lymph nodes could be felt in his neck, and the ones in his axillae and groins were much smaller; the spleen was enlarged only 1 in. (2.5 cm.) below the costal margin and the liver was not palpable. Four months later very tiny nodes could be felt in his groins but none elsewhere, and the liver and spleen were not palpable. He has remained well, with no lymphadenopathy and a normal blood count for three and a half years.

Reticulosarcoma

Two male patients, aged 50 and 30 years respectively, with reticulosarcoma have been treated with uracil mustard.

Case Reports

A 50-year-old taxi proprietor had first noticed enlarged nodes in his neck, which on biopsy showed reticulosarcoma. He was treated with chlorambucil and later mannomustine and blood transfusions. A year after he was first seen he still had enlarged lymph nodes up to 3 cm. across in the left side of his neck and his blood count showed: Hb 11.7 g., white cells 6,700, and platelets 50,000. He was given uracil

mustard 2 mg. daily and continued to have occasional blood transfusions as required. After 12 weeks the dose was raised to 3 mg. daily as the nodes were enlarging, his haemoglobin being 11.2 g., white cells 2,850, and platelets 22,000. He developed some pain in his back, requiring hospital admission, but no lesions were seen in his spine. His general condition deteriorated and the nodal mass remained unchanged. He died 18 weeks after first receiving uracil mustard.

The second patient, a cotton-mill worker, had had pain under his left ribs and anorexia for six months when first seen. His spleen was enlarged 3 in. (7.5 cm.) below the left costal margin and was irregular in shape and firm. There were a few enlarged nodes in his groins: biopsy of one revealed reticulosarcoma. He was treated with intravenous trimustine and the spleen and lymph nodes decreased a little in size; he was also given prednisolone. After 10 months further trimustine did not reduce the size of his spleen, which was still enlarged about 3 in. (7.5 cm.); the liver was also enlarged about 2 in. (5 cm.), and he now had enlarged nodes in the neck and axillae as well as his groins. His blood count was: Hb 10.5 g., white cells 6,600, and platelets 219,000. He was given uracil mustard 5 mg. daily for one week. The platelet count had fallen to 64,000 by this time, and two weeks later it was 16,000. The white-cell count fell to 200, and after four weeks the uracil mustard was stopped. Two months later his blood count was: Hb 11.4 g., white cells 10,800, and platelets 148,000. His spleen was still enlarged about 3 in. (7.5 cm.) and was very hard. Nodes were present in his groins, and his liver was just palpable. He was put back on to uracil mustard 5 mg. daily, and in all took 250 mg. over the next five weeks. His liver and spleen were much smaller and the inguinal nodes impalpable (Hb 9.3 g., white cells 1,200, platelets 8,000). Four weeks later his liver and spleen were only just palpable and his count showed: Hb 6.9 g., white cells 2,900, and platelets 61,000.

Large doses of uracil mustard did reduce the enlarged lymph nodes and spleen, but in the second case they resulted in depression of the white cells and platelets. Smaller doses in both these patients seemed to produce little or no benefit.

Carcinoma of Bronchus

Ten patients (8 males, 2 females) aged 32 to 72 years with carcinoma of the bronchus have been treated with uracil mustard. The diagnoses in nine were confirmed histologically: three had squamous-cell carcinomata, three oat-cell carcinomata, and three were undifferentiated. All cases had been considered by the thoracic surgeon to be inoperable, although one had already had a lobectomy. Uracil mustard was given in doses of from 1 mg. on alternate days to 5 mg. daily, and the duration of treatment varied between 2 and 40 weeks. Most of the patients were quite ill when treatment was begun and little improvement in the general clinical condition of most of them was noted, nor was any marked reduction in the sizes of the carcinomata observed either clinically or on x-ray examination of their chests, although in two patients the malignant process appeared to be slowed quite obviously for a time. Eight of the patients died within five months of starting treatment, while the other two lived for more than nine months without any increase in the size of the neoplastic masses according to the chest x-ray examination.

Toxic Reactions

Toxic reactions were very infrequent. Although the platelet count was often reduced to low figures, bleeding was rarely seen, and in some of the patients with acute leukaemias the low platelet counts were most probably due to the original disease. Some purpura was noted in

12 of the 20 patients whose platelet counts fell below 20,000; but in general, although some lowering of the platelet count was usually seen when uracil mustard was given, this was regarded as an inevitable side-effect rather than an indication to stop treatment. If the platelet counts showed progressive diminution to levels much below 100,000 the uracil mustard was reduced in dosage or temporarily stopped and prednisolone given, when the platelet counts usually rose quickly to nearer normal levels.

Seven patients experienced slight gastro-intestinal side-effects—four having slight vomiting and three nausea—which were completely alleviated by reducing the dose from 5 to 1 mg. daily or by temporary discontinuance. In only two patients was the vomiting severe enough to require temporary cessation of treatment. Shanbrom *et al.* (1960) observed gastro-intestinal symptoms in 41 of their 130 patients given uracil mustard; 12 had skin changes (including two with some alopecia), but these subsided when the drug was stopped and did not recur when it was restarted. Kennedy and Theologides (1961) noted anorexia in 5, nausea in 14, and vomiting in a further 16 of 49 patients treated with uracil mustard, while Spurr and Hayes (1960), out of 18 patients given the drug, noted four with gastro-intestinal symptoms and one with a rash.

Discussion

The search for an equally efficient oral substitute for the intravenously administered nitrogen mustards, such as tri-(2-chlorethyl)amine hydrochloride, has led to the trial of a new substance, 5-di-(2-chlorethyl)aminouracil (uracil mustard), that had been synthesized by Lyttle and Petering (1958).

We have had the opportunity of carrying out clinical trials of this preparation during the last four years in the treatment of 91 patients suffering from chronic myeloid (21) and lymphatic leukaemias (18), acute leukaemia (6), polycythaemias (5), Hodgkin's disease (28), Brill-Symmers's disease (1), reticulosarcomata (2), and carcinoma of the bronchus (10).

Uracil mustard is easy to control, is given orally, and is singularly free from toxic side-effects. One of the striking points is that when given orally it behaves in the same way that the nitrogen mustards do when given intravenously for the chronic myeloid and lymphatic leukaemias, Hodgkin's disease, and reticulososes, and in acute leukaemias when there are high white-cell counts. The dosage employed was simple, varying from 1 to 5 mg. daily, with gradual reduction to 1 mg. weekly or fortnightly.

In 21 patients with chronic myeloid leukaemia we found that the hepatomegaly, splenomegaly, and the leucocytosis all diminished rapidly, while the liver returned to its normal size and the spleen became minimal or impalpable. The platelets slowly diminished in numbers if the dosage was maintained at too high a level for too long, and in five patients there were less than 20,000, but by carefully controlling the period and dosage of treatment this fall could be easily prevented and did not constitute a major problem. Thus in this four-year trial series of 21 patients nine lived for 18 months, five for over three years, and two for three and a half to four years. Somewhat similar results were obtained by Shanbrom *et al.* (1960) in 13 patients observed over a period of 6 to 11 months, although a number of side-reactions of moderate degree did occur.

In 18 cases of chronic lymphatic leukaemia we observed similar good results, with reduction in the splenomegaly, hepatomegaly, and general lymphadenopathy.

The increased leucocyte counts were eventually reduced to the desired levels by adjusting the dosage and duration of treatment as above, while the platelets fell to 20,000 in seven patients but no bruising or bleeding occurred. These results with chronic lymphatic leukaemia were very striking, as has been noted also by Shanbrom *et al.* (1960), by Kennedy and Theologides (1961), and by Spurr and Hayes (1960) (Table IV).

TABLE IV.—Results of Treatment with Uracil Mustard

Author	Chronic Myeloid Leuk-aemia		Chronic Lym-phatic Leuk-aemia		Acute Leuk-aemia		Hodgkin's Disease		Toxic Effects (%)	
	No.	C.I.	No.	C.I.	No.	C.I.	No.	C.I.	G.I.	Others
Shanbrom <i>et al.</i> (1960)	13	11	21	14	5	1	31	16	31.5	14.6
Spurr and Hayes (1960)			7	5			1	1	22.2	5.5
Kennedy and Theologides (1961)			20	15			14	8	21	
Lane <i>et al.</i> (1960)	1	1					6	3		
Porter <i>et al.</i> (1962)					11	0			82	
Present authors	23	23	18	18	6	*	28	18	7.5	1.1

* Leucocytosis reduced in 6. Lymphadenopathy reduced in 1.
C.I. = Clinical improvement. G.I. = Gastro-intestinal.

The acute leukaemias ordinarily do not lend themselves to this form of treatment, except when the white-cell count is high, and then uracil mustard will produce a marked and rapid reduction in the white-cell count to the required level; but in the six such patients little other clinical or objective improvement was noted after this treatment. Shanbrom *et al.* (1960) and Porter *et al.* (1962) commented similarly on the poor results obtained in acute leukaemia with uracil mustard.

When uracil mustard was given to five patients with primary polycythaemia vera we noted definite improvement in only one, and do not consider that it has any place in the treatment of this disease. Shanbrom *et al.* (1960) thought they had observed some objective improvement in four cases.

The treatment of Hodgkin's disease was very encouraging in 28 patients given uracil mustard. We feel that this drug is safe, mild, and very efficient, and equal to any other treatment we have used in the past over similar intervals of time. Twenty-four of these patients had greatly enlarged peripheral lymphatic nodes and 17 showed complete regression after treatment, while 18 of the 28 showed marked objective improvement while on continuous or intermittent courses of uracil mustard; 13 patients have lived for over 18 months, and seven who had been on treatment for more than two years are very well. These types of results have been obtained by Shanbrom *et al.* (1960), Lane *et al.* (1960), and Kennedy and Theologides (1961) over much shorter periods of time.

One patient with Brill-Symmers's disease responded extremely well with complete symptomless and objective improvement after one course of uracil mustard of two weeks' duration and has remained in good health and free from any signs of recurrence for three and a half years. Shanbrom *et al.* (1960) (two patients) and Spurr and Hayes (1960) (one patient) also had similar results. One of our two patients with reticulosarcoma showed marked improvement, with diminution in the size of the

lymph nodes, on large doses of uracil mustard. Similar improvement was noted by Lane *et al.* (1960) in the one patient with reticulosarcoma they treated, by Shanbrom *et al.* (1960) in one out of two, and by Spurr and Hayes (1960) in the only one they treated.

In general we have been very impressed with the value of uracil mustard in the treatment of the above conditions, for it is the first substance to be given orally in these groups of diseases with the same remarkably rapid and effective results as are associated with intravenously given nitrogen mustards, results first observed by Wilkinson in 1941-2.

Side-reactions to uracil mustard have very seldom occurred, and then only of minor degree. In some 7.5% of our patients slight nausea and, very rarely, vomiting or slight diarrhoea were noted, but always after doses of 5 mg. daily for about 10 to 14 days. These were immediately and completely resolved on stopping the treatment for a few days or by reducing the dose to 1-3 mg. daily.

Summary

Clinical trials on 91 patients over a period of four years have been made of a new substance, 5-di-(2-chlorethyl)aminouracil (uracil mustard; U8344).

Uracil mustard in small doses is very effective in the treatment of chronic myeloid leukaemia and chronic lymphatic leukaemia and in maintenance; it produces rapid regression in the size of the spleen, liver, and lymph nodes, and a return to normal levels of the white cells.

Uracil mustard is of no value in the treatment of acute leukaemia but will reduce the white-cell count in those patients in whom it is raised.

It is of little value in the treatment of polycythaemia vera.

Hodgkin's disease and reticulososes respond very well indeed to uracil mustard given orally, and patients have been maintained in good condition for periods up to three and a half years on small doses.

In all these cases red-cell counts and haemoglobins are not particularly affected, but the platelets are diminished if the dosage of uracil mustard is kept at too high a level for too long; but this can be prevented or controlled by careful supervision of the dose and by regular blood counts.

Side-effects of treatment with uracil mustard are not common or severe, but 7.5% of our patients had some gastro-intestinal disturbances on the doses of 5 mg. daily after 10 to 14 days, but not on smaller doses.

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