cord haemoglobin level suggests and early exchange transfusion is indicated.

There were, in addition to the 80 pairs of cases described, 50 infants with cord haemoglobin values over 11.5 g./100 ml. but who were treated within the first nine hours of life. Evidence has already been presented indicating that exchange transfusion was performed in the first nine hours in some of these either because the cord haemoglobin value was relatively low or because early jaundice developed. In many, however, the time of exchange transfusion and whether or not the case was paired was determined by chance. The subsequent course in these cases did not differ from either of the paired groups. The same proportion developed severe jaundice, a similar number required additional transfusion, and only one infant died, not from haemolytic disease but from hyaline membrane disease. Six of the 50 infants were upset by the transfusion itself, a slightly higher proportion than in either of the other two groups.

Even where haemolytic disease of the newborn has not been predicted, relatively severe disease should be diagnosed within 24 hours of birth, and if prompt exchange transfusion is carried out satisfactory results should be achieved.

Summary

During 1958, 1959, and 1960 we performed exchange transfusion between 9 and 24 hours in 80 infants in whom the cord haemoglobin values exceeded 11.5 g./100 ml. From the same period we selected 80 infants treated between one and nine hours but who were otherwise similar with regard to birth weight and cord haemoglobin and cord bilirubin levels.

Although jaundice was more common in the group treated after nine hours, the frequency of severe jaundice or bilirubinaemia exceeding 15 mg./100 ml. was the same in the two groups, as was the need for subsequent exchange transfusion. There was a suggestion that the infants treated later tolerated the procedure better.

No death attributed to haemolytic disease of the newborn occurred in either group.

We conclude that if the cord haemoglobin value exceeds 11.5 g./100 ml. in the absence of clinical or other evidence of severe haemolytic disease exchange transfusion may safely be delayed up to 16 hours of life.

Acknowledgments are made to the medical and nursing staff of the hospitals concerned, to the staff of the National Blood Transfusion Service, and in particular to Dr. Sheila Murray and Dr. George Knox for comments and helpful criticism.

This study has been partly financed by a grant from the Dowager Countess Eleanor Peel Trust.

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The London County Council is to resume the recruitment of women ambulance drivers. The service is at present short of 80 drivers—770 are employed but 850 are needed. There is a high rate of wastage and the demands on the service are increasing: 243,342 patients were carried in 1947, 803,134 in 1953, and 1,356,965 in 1960.

CYCLOPHOSPHAMIDE IN TREATMENT OF DISSEMINATED MALIGNANT DISEASE

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A clinical trial has been undertaken at St. George's Hospital since November, 1959, using a new alkylating agent known as cyclophosphamide ("endoxan," "endoxana," "cytoxan"). This drug was first synthesized in 1958 with the specific purpose of preparing a form of nitrogen mustard which would be inactive when administered and activated only on reaching the site where its therapeutic effect was required. Toxic side-effects should be reduced and tolerance to the drug thereby improved.

Malignant cells are known to be rich in phosphatases and phosphamidases. With this in mind, Arnold and Bourseaux (1958) and Arnold *et al.* (1958) synthesized a number of nitrogen mustard phosphamides and phosphamide esters in the hope that they would be split by these enzymes to an active form within the tumours.

Cyclophosphamide is one of these "transport-form/active-form" compounds. It is a cyclic nitrogen mustard phosphamide ester, belonging to the group of diamide-mono-esters. Arnold *et al.* (1961) consider it to be inert *in vitro* and highly effective *in vivo*. The chemical formula is as follows:

Choice of Cases.—Ninety-two cases with widespread malignant disease have been treated since November, 1959. All these patients were either beyond the scope of conventional forms of therapy or had suffered recurrences after surgery, irradiation, nitrogen mustard, or hormone therapy. Treatment has been undertaken even in the most advanced stages of disease.

Method of Treatment

The recommendations of the German workers (Gross and Lambers, 1958) have been followed in estimating dosage: the amount given has been regulated by the effect of the drug on the haemopoietic system. As a general rule therapy has been started by the intravenous route—with an initial test dose of 100 mg. and subsequent daily doses of 200 mg. intravenously. On occasion this has been increased to 300 mg. and sometimes even 400 mg. daily if there has been no reduction of the circulating white-cell count within five days. This dose has never been exceeded on any one day—except on one occasion, to which reference will be made later.

A deliberate attempt has been made to bring the total white-cell count down to 2,000/c.mm. in order to obtain a maximal anti-tumour effect. It is felt that anything

less drastic is likely to be ineffectual. Less encouraging results reported by other workers may partly be due to inadequate dosage. Intravenous therapy is given until the white-cell level approximates 2,000/c.mm. This usually takes between 7 and 14 days. Oral administration of the drug is then adopted, amounting to 100–200 mg. daily in divided doses to maintain the circulating white-cell count between 2,000 and 3,000/c.mm.; this is continued indefinitely as a maintenance therapy. Some patients may require only 50 mg./day.

Other routes of administration have been used—intraleural, intraperitoneal, and into the tumour itself—care being taken not to exceed the total dosage of 500 mg. in any one day. Perfusion has not been used in this series.

Initial treatment has nearly always been carried out on in-patients. In the early stages white-cell estimations were made on alternate days. Subsequently, patients who were discharged from hospital on maintenance therapy attended once a week for a routine haematological check, and, if necessary, the dose was adjusted accordingly. On full stabilization this period was extended to one month. Some of the patients in this series have received the drug for more than a year.

The drug is supplied in powder form for intravenous use and is dissolved in sterile water immediately before injection. Oral administration is by tablet.

In order to assess the activity of cyclophosphamide, it has been used alone wherever possible, and not in conjunction with other forms of treatment. Where other therapy overlapped, such cases have not been included in the series: for instance, those patients who were receiving irradiation in conjunction with cyclophosphamide have been excluded, as any improvement may well have been due to the irradiation. The only exceptions to this rule were two patients with carcinoma of the breast who had been receiving hormones (prednisone and testosterone) for some months previously but had relapsed.

Method of Clinical Assessment

The results in any such series are very difficult to judge, particularly if this evaluation is undertaken by many different observers. Moreover, the assessment of subjective improvement is unreliable. The mere fact of admission to hospital often leads to improvement without any treatment.

An attempt was made for all the treated cases to be seen by one or both of two independent observers, and *objective* findings were recorded—such as size of tumour, visible or palpable secondary deposits, and radiological changes in lungs and bones when relevant. Criteria of general well-being, lethargy, pain, nausea, loss of appetite, etc., were noted and any improvement was recorded as *subjective* improvement. The final assessment has been tabulated under these two headings (see Table I).

In an attempt to overcome some difficulties of assessment the method of the mean clinical value introduced by Walpole and Paterson (1949) has been used. Every lesion is allocated a different figure according to whether it remains unchanged, improves, or deteriorates. These marks are estimated at four-weekly intervals, added together, and divided by the number of lesions being assessed. The final figure is then plotted on a graph and the progress of a patient may be seen at a glance (Fig. 1).

Results

Of the 92 patients treated, 16 were excluded for one of the following reasons: (1) drug received for less than two weeks—treatment was regarded as inadequate; (2) documentation was insufficient or follow-up was not possible; and (3) other forms of treatment were used simultaneously.

The remaining 76 cases were assessed (Table I), diagnosis having been confirmed in all instances.

FIG. 1.—Showing initial temporary improvement for an eight-week period and subsequent deterioration and death. This is a typical pattern in those who responded to cyclophosphamide.

TABLE I.—Objective and Subjective Responses to Cyclophosphamide in 76 Cases. Subjective Response Shown in Parentheses

Tumour	No. of Cases	No Response	Response for (Months):				
			<3	3–6	6–9	9–12	12+
Carcinoma of breast ..	20	11	2		1	1 (2)	2 (1)
" " bronchus ..	27	18	2 (1)	6			
" " pancreas ..	2	2					
" " ovary ..	1	1					
" " prostate ..	1	1					
" " cervix ..	1	1					
" " rectum ..	1	1					
Malignant melanoma ..	1	1					
Hypernephroma ..	1	1					
Carcinomatosis ..	1	1					
Sarcoma ..	3	1	1			1	
Reticulum-cell sarcoma ..	4	1	1	2			
Lymphosarcoma ..	4	4					
Hodgkin's disease ..	5		1 (1)	1 (1)	1	1	
Mycosis fungoides ..	1		1				
Myelomonocytic leukaemia ..	1	1					
Multiple myelomatosis ..	2			(2)			

It is impracticable to discuss all aspects of individual patients. Diseases which showed some response to treatment have been selected for discussion: (1) carcinoma of the breast, (2) carcinoma of the bronchus, (3) malignant lymphoma, (4) sarcoma, and (5) multiple myelomatosis. These are illustrated by selected case reports.

Carcinoma of Breast

Most of the 20 patients in this group had previously received other forms of treatment—surgery, irradiation, and hormone therapy—but had since relapsed (Table II).

Three very advanced cases were treated with cyclophosphamide as an initial measure: none of these

responded. However, of the 20 patients, six showed objective improvement and a further three subjective improvement.

Case 1.—A woman aged 48 had a mastectomy in February, 1958, followed by deep x-ray therapy for carcinoma of the breast. In June, 1959, skeletal metastases appeared. For these she had ovariectomy, prednisone, and subsequent androgen therapy. After an initial response she relapsed and was readmitted in November complaining of malaise and lethargy, and was bedridden owing to severe pain in her back, pelvis, and hips. Radiographs showed extensive osteolytic metastases of lumbar spine, pelvis, and skull. In December cyclophosphamide was begun. She responded very well indeed, and returned to her business and was able to go for long walks. Radiographs of the skeletal system showed recalcification of the carcinomatous deposits (Fig. 2). She was symptom-free 18 months later.

Case 3.—A woman aged 50 had pre-operative deep x-ray therapy and subsequent left-sided simple mastectomy in January, 1959. In February, 1960, she presented with fixed hard glands in the adjacent axilla and a brawny lymphoedema. A chest radiograph showed a left pleural effusion and a pathological fracture of the fourth, fifth, and sixth ribs. She also had deposits in the spine and pelvis. Cyclophosphamide therapy reduced the size of the glands and diminished the oedema of the arm. Radiographs showed resorption of the pleural effusion and recalcification of bone. She returned to a full day's work and led an active normal life until she relapsed and died 15 months after starting treatment.

Case 4.—A woman aged 58 had a radical mastectomy for cancer of the breast in 1957. In 1959 a local recurrence was treated with prednisone and ovariectomy. In January, 1960, she had multiple skin nodules, one of which was biopsied. A diagnosis of secondary carcinoma was confirmed. She also had severe back pain. Radiographs of the spine revealed osteolytic metastases. Cyclophosphamide

FIG. 2.—Case 1. Radiograph of pelvis (above) before (December 8, 1959) and (below) after (February 10, 1961) treatment with cyclophosphamide. Note recalcification of secondary deposits, especially in right pubic bone.

TABLE II.—*Carcinoma of Breast (20 Cases)*

Case No.	Age and Sex	Previous Treatment	Cyclophosphamide Treatment. Routes of Administration	Side-effects			Clinical Features	Response	
				Alopecia	W.B.C. below 1,000/c.mm. at Some Time	Severe Marrow Failure		Duration	Assessment
1*	48 F	S, X, H	I.V., oral	++	+	—	Continued regression of pulmonary and bone metastases	18+ months	Objective
2	56 F	S, X, H	"	++	—	—	Regression of metastases in spine and skin, then relapse	12 "	"
3*	50 F	S, X	"	+	+	—	Improvement of left arm lymphoedema, left pleural effusion, and bone metastases—relapse	11 "	"
4*	58 F	S, H	"	++	+	—	Disappearance of skin nodules and regression of spine metastases—relapse	8 "	"
5	56 F	X, H	"	+	—	—	Regression of left arm lymphoedema, axillary glands, and skin metastases—relapse	2 "	"
6*	61 F	S, X	"	++	—	—	Recovery from coma and left hemiplegia due to cerebral metastases. Death due to pulmonary embolus	2 "	"
7	59 F	S, X	"	++	—	—	Recovery from drowsiness, vertigo, nausea, and vomiting due to cerebellar secondary	13+ "	Subjective
8	51 F	S, X, H	"	++	+	—	Breathlessness improved. No change in metastases in glands, bones or lungs—relapse	10 "	"
9	52 F	S, X	"	++	—	—	Breathlessness improved. No change in pleural effusion—relapse	9 "	"
10	60 F	—	"	—	—	—	No change in primary lesion or metastases in glands, lungs, or brain		Nil
11	56 F	S, X	"	+	—	—	No change in bone metastases		"
12	59 F	S, X, H	"	+	+	—	" " " pleural effusion or metastases in glands, chest wall, or skin		"
13	51 F	X	"	—	—	—	No change in primary, glands, or pleural effusion		"
14	49 F	S, X, H, thiotepea	"	+	+	—	" " " pleural effusion or lung metastases		"
15	56 F	—	"	+	—	—	" " " bone metastases		"
16	56 F	—	"	+	+	+	" " " primary. Recovered from marrow failure after temporary cessation of treatment		"
17	74 F	S, X	Oral	—	+	—	No change in bone metastases		"
18	52 F	X	I.V., oral	—	—	—	" " " primary or pleural effusion		"
19	54 F	S, X	"	—	+	—	" " " hepatic metastases or ascites		"
20	49 F	S, X, H	"	—	+	—	" " " local recurrence, pleural effusion, or bone metastases		"

S=Surgery. X=Irradiation. H=Hormonal therapy. * See case reports in text.

was given and an excellent response obtained. The skin nodules regressed completely. Her pain was relieved. She suffered from complete alopecia. She was alive and well nine months after starting treatment.

Case 6.—A woman aged 61 had a left radical mastectomy for cancer of the breast in July, 1959, followed by deep x-ray therapy. In November she was readmitted in a semicomatose state with a left hemiplegia which had been developing over the previous two weeks, thought to be due to a cerebral secondary deposit. Cyclophosphamide was given, with a dramatic response. She recovered consciousness and returned to a normal mental state. She regained full use of her paralysed arm and leg, and after six weeks of treatment was able to walk out of the hospital. She died quite suddenly in March, 1960. Necropsy revealed that death was due to a massive pulmonary embolus. The cerebral secondary was confirmed and histological section revealed areas of necrosis.

Carcinoma of Bronchus

Eight of the 27 patients treated showed objective signs of improvement and a further case showed subjective improvement although there was no x-ray change (Table III).

Case 21.—In April, 1960, a man aged 65 was admitted to hospital in a moribund state with multiple metastatic skin nodules from a primary bronchogenic carcinoma. Cyclophosphamide produced a dramatic response. The skin lesions disappeared (Fig. 3). His general condition improved and he was discharged five weeks after starting treatment. At four months his condition was unchanged, but five months after starting treatment he was readmitted with a temperature of 102° F. (38.9° C.), signs of bronchopneumonia, and a peripheral white-cell count of 700/c.mm. Cyclophosphamide was stopped. Despite antibiotics he died two days later without evidence of bone-marrow recovery. Necropsy revealed staphylococcal pneumonia and confirmed the presence of an oat-celled carcinoma of the bronchus.

Case 23.—A man aged 40 presented in February, 1960, with superior vena caval obstruction and pain in right chest. Bronchoscopy confirmed carcinoma of the bronchus. Biopsy revealed undifferentiated oat-cell carcinoma. Cyclophosphamide was started. Two months later he had no caval obstruction and no pain. Four months later he was "very well, playing cricket and back at work." But five months after starting treatment there was recurrence of S.V.C. obstruction and he died in September, 1960.

Case 24.—A man aged 55 with carcinoma of the bronchus presented in February, 1960, with shortness of breath,

TABLE III.—Carcinoma of Bronchus (27 Cases)

Case No.	Age and Sex	Previous Treatment	Cyclophosphamide Treatment. Routes of Administration	Side-effects			Clinical Features	Response	
				Alopecia	W.B.C. below 1,000/c.mm. at Some Time	Severe Marrow Failure		Duration	Assessment
21*	65 M	—	I.V., oral	+	+	+	Regression of pleural effusion and skin metastases. Death due to staphylococcal pneumonia associated with marrow failure. P.M. showed further metastases	5 months	Objective
22	64 M	X	I.V., oral, intrapleural	+	+	—	Improvement in pleural effusion and metastases in chest wall. Chest pain diminished—relapse	4 "	"
23*	40 M	—	I.V., oral	+	—	—	Improvement of chest pain, S.V.C. obstruction, gland metastases, and primary lesion (radiograph)—relapse	4 "	"
24*	55 M	—	"	+	+	—	Regression of oedema left arm and chest wall, pleural effusion, and primary (radiograph)—relapse	3 "	"
25	67 M	—	I.V., oral, intrapleural	—	+	—	Pleural effusion and liver metastases improved—relapse	3 "	"
26	54 M	—	I.V., oral	++	—	—	Headaches due to cerebral metastasis improved. Slight improvement of primary lesion (radiograph)—relapse	3 "	"
27	47 M	S, X	"	+	—	—	Improvement of S.V.C. obstruction. Chest pain and breathlessness. No change in mediastinal glands—relapse	2 "	"
28	60 M	X	"	+	+	+	Improvement in fits and paresis due to cerebral metastases and in primary (radiograph). Died after marrow failure with haemorrhage. P.M. revealed progressive metastases	1 month	"
29	49 F	X	I.V., oral, intrapleural	++	+	—	Improvement of headaches and vomiting due to cerebral metastases	1 "	Subjective
30	60 F	—	I.V., oral	++	—	—	No change in cough, pain, gland metastases, or radiographic changes	Nil	
31	46 M	—	"	—	+	+	No change in pleural effusion or liver metastases. Died with marrow failure and widespread disease	"	
32	34 F	—	I.V.	—	—	—	No change in primary, lymph node, or haemoptysis	"	
33	57 M	—	I.V., oral	—	—	—	No change in primary, skin metastases, chest pain, or dyspnoea	"	
34	49 M	—	I.V.	—	—	—	No change in primary, bone metastases, chest pain, or dyspnoea	"	
35	62 F	—	I.V., oral	+	—	—	Primary and metastases in glands, liver, and skin all uninfluenced	"	
36	70 M	—	I.V., oral, intrapleural	—	—	—	No change in pleural effusion or pain	"	
37	55 M	X	"	++	—	—	No effect on pleural effusion, pain, breathlessness, or liver metastases	"	
38	52 M	X	I.V., oral	++	—	—	Primary and glandular metastases unaffected	"	
39	43 F	—	"	—	—	—	No change in primary, pleural effusion, or gland metastases	"	
40	52 F	—	I.V.	—	—	—	Primary and metastases uninfluenced	"	
41	65 M	—	I.V., oral, intrapleural	—	—	—	Primary, pleural effusion, and glands unchanged	"	
42	51 M	—	"	+	—	—	No "benefit" upon "hemiparesis" due to "cerebral metastases or primary"	"	
43	58 M	—	I.V., oral	—	—	—		"	
44	54 M	—	"	+	—	—	Primary and metastases uninfluenced	"	
45	76 M	—	"	+	+	—	Primary and metastases in glands and skin all uninfluenced	"	
46	56 M	—	"	+	—	—	Primary and widespread metastases unchanged	"	
47	60 M	—	I.V., oral, intrapleural	+	+	—	" " chest pain uninfluenced	"	

S=Surgery. X=Irradiation. * See case reports in text.

oedema left arm and left chest wall, severe clubbing, and a liver enlarged four fingerbreadths below the costal margin. Radiograph revealed a shadow in the left upper lobe and a large effusion. Cyclophosphamide started: resolution of the mass on radiograph, complete resorption of the effusion, improvement of general health. He relapsed after three months' treatment and died in July, 1960.

FIG. 3.—Case 21. Metastatic skin nodule from primary carcinoma of bronchus (left) before (April 14, 1960) and (right) after (June 30, 1960) treatment with cyclophosphamide.

Malignant Lymphomas

In this series the following conditions were included under this heading—reticulum-cell sarcoma, lymphosarcoma, Hodgkin's disease, and mycosis fungoides. A total of 14 patients have been treated. Seven showed objective signs of improvement and two others were improved subjectively. Table IV gives details for each subgroup.

Case 49.—A man aged 60 presented in December, 1959, with lymphadenopathy involving cervical, axillary, and inguinal glands. The liver was enlarged four fingerbreadths below the costal margin. Spleen was also palpable. The bone-marrow showed involvement by Hodgkin's disease. He was a very ill man. He had received no other treatment. Cyclophosphamide was given as initial therapy with an excellent response. His general health and appetite improved and his weight increased. All the enlarged glands were reduced in size, showing a marked improvement after only two weeks. He suffered from alopecia. Long-term therapy was continued and he showed no sign of active disease for seven months, but thereafter he relapsed and died nine months after starting treatment.

Case 50.—A man aged 47, a proved case of Hodgkin's disease, was treated in 1958 with mustine (HN2). In January, 1960, he presented with lassitude, apathy, and generalized lymphadenopathy involving glands in the neck, axillae, and both groins. Liver and spleen were enlarged. Cyclophosphamide produced an excellent response, and by the end of four weeks all the glands had disappeared except for two small nodules less than $\frac{1}{4}$ in. (6 mm.) in diameter. Liver and spleen regressed and were impalpable. Oral therapy was continued, but he suffered a relapse in May, 1960, while still on the drug. Dosage was increased, but he failed to respond and died six months after the beginning of cyclophosphamide therapy.

Case 53.—A man aged 73 presented in March, 1960, with multiple skin lesions involving head, trunk, arms, and legs. He also had a liver enlarged four fingerbreadths below the costal margin. Biopsy showed a reticulum-cell sarcoma. Cyclophosphamide was given with an initial dramatic response. The lesions faded rapidly (Fig. 4). Dosage in this case was higher than usual and increased to 400 mg. a day intravenously. In the third week there was marrow failure, W.B.C. 250/c.mm. Cyclophosphamide was stopped.

TABLE IV.—*Malignant Lymphoma (14 Cases)*

Case No.	Age and Sex	Previous Treatment	Cyclophosphamide Treatment. Routes of Administration	Side-effects			Clinical Features	Response		
				Alopecia	W.B.C. below 1,000/c.mm. at Some Time	Severe Marrow Failure		Duration	Assessment	
Hodgkin's Disease										
48	57 F	X, thiotepe	Oral, intrapleural	+	+	—	Regression of enlarged glands and of pleural effusion. Liver became smaller—relapse	10 months	Objective	
49*	60 M	—	I.V., oral	+	—	—	Glands, liver, and spleen all became smaller. General health improved—relapse	6 „	„	
50*	47 M	HN2	„	+	—	—	Improvement in glands, liver, spleen, and general health—relapse	3 „	„	
51	40 M	X	Oral	+	—	—	General health improved. Temperature returned to normal and weight increased—relapse	3 „	Subjective	
52	55 M	X, HN2, T.E.M.	I.V., oral	+	+	—	Improvement of pain due to enlarged glands in pelvis and of pyrexia—relapse	2 „	„	
Reticulum Cell Sarcoma										
53*	73 M	—	Oral	+	+	—	Complete disappearance of multiple skin nodules—relapse	8 „	Objective	
54	40 M	—	I.V., oral	+	—	—	Regression of glands and improvement of general health	5 „	„	
55	35 M	—	I.V.	+	—	—	Complete disappearance of all glands. Death due to meningitis. P.M.—no evidence of lymphoma	1 month	„	
56	64 M	X, S	I.V., oral	—	—	—	No change in oedema of leg or enlarged inguinal glands		Nil	
Mycosis Fungoides										
57	67 F	X, S	Oral	—	+	+	Complete disappearance of skin nodules. Death due to septicaemia associated with marrow failure	2 weeks	Objective	
Lymphosarcoma										
58	46 M	X, CB1348	I.V.	—	—	—	No effect on enlarging glands		Nil	
59	62 M	—	—	—	—	—	Involvement of liver unaffected		„	
60	60 M	X, S, thiotepe	I.V., oral	+	—	—	No change in glands or liver		„	
61	19 M	—	I.V.	—	—	—	Skin metastases unaffected. HN2 also not beneficial		„	

X=Irradiation. S=Steroid therapy. * See case reports in text.

The anaemia and thrombocytopenia were treated with fresh-blood transfusion. Subsequently oral therapy with cyclophosphamide was able to be started. Three months after initial treatment he developed new lesions. He gradually deteriorated and died six months from the time when he was first seen.

Sarcoma

Three patients with sarcoma were treated. Two, suffering from fibrosarcoma of the breast and neurofibrosarcoma of the leg, showed objective improvement.

Case 62.—A girl aged 18 presented in May, 1959, with tumour of the breast which on biopsy was found to be fibrosarcoma (Table V). Mastectomy was performed. Deep x-ray therapy was given before the mastectomy. She subsequently developed multiple metastases in the lung fields and a right-sided pleural effusion. Cyclophosphamide was started in October, 1959. There was a gradual regression of all lesions over a period of six weeks as shown by radiography. She developed alopecia. However, she relapsed after this and her condition rapidly deteriorated. A pleural effusion appeared on the left side, although the lesions had almost disappeared on the right (Fig. 5). On two occasions 1 g. of cyclophosphamide was given intrapleurally in addition to her oral dose, but did not have any effect upon the disease. She developed an intercurrent infection and died with a white-cell count of only 50/c.mm. Reinfusion of the patient's own bone-marrow that had been removed before treatment and stored at -78°C . failed to assist marrow recovery. Necropsy showed extensive disease, but her death was accelerated by marrow aplasia due to excessive dosage. This was the first case treated in this series, and such a large dose has since been avoided.

Multiple Myelomatosis

Two patients were treated. Both experienced lessening of bone pain but without improvement of x-ray appearances.

Side-effects

Alopecia.—This developed in approximately 60% of cases after three to four weeks of treatment, resulting in complete baldness in approximately one-quarter of all the patients treated. It is a distressing feature, particularly to women. In the majority of patients who survived there was a new growth of hair while on maintenance therapy, but it was often stunted and a wig was necessary. All patients who were given this drug

were warned of this consequence before starting treatment.

Bone-marrow Failure.—A deliberate attempt was made to reduce the total white-cell count to approximately 2,000/c.mm. as an indication of effective dosage. In some cases, however, it fell even further. As any patient whose white-count fell to 1,000/c.mm. or less was thought to be subject to danger, the routine adopted was to stop the drug, give wide-spectrum antibiotics, and, if necessary, a fresh-blood transfusion. Experience has shown that if the patient survives, the white-cell count will recover spontaneously within four to seven

FIG. 4.—Case 53. Skin lesions in patient with reticulum-cell sarcoma (left) before (February 19, 1960) and (right) after (April 6, 1960) treatment. Subsequently, however, he developed further lesions and gradually deteriorated.

days of stopping the drug. This difference between cyclophosphamide and other drugs closely related is not yet explained (Pegg, 1960), but is an undoubted advantage of cyclophosphamide. Altogether there were 28 cases (37%) whose white-cell count fell below 1,000/c.mm. In all but five recovery of bone-marrow function occurred, but in these five death occurred with marrow aplasia and an overwhelming infection. In four of these patients the lesions were not responding to the drug and they would have succumbed to their disease within a very short time; the remaining patient, however, died two weeks after starting treatment while her lesions were undergoing a marked regression. In most patients there was some fall of haemoglobin level

TABLE V.—Sarcoma (3 Cases)

Case No.	Age and Sex	Previous Treatment	Cyclophosphamide Treatment. Routes of Administration	Side-effects			Clinical Features	Response		
				Alopecia	W.B.C. below 1,000/c.mm. at Some Time	Severe Marrow Failure		Duration	Assessment	
Fibrosarcoma of Breast										
62*	18 F	S, X	I.V., oral, intrapleural	+	+	+	Regression of pulmonary metastases and recurrence in chest wall. Death associated with marrow failure and widespread disease	2 months	Objective	
Neurofibrosarcoma										
63	52 F	S	I.V., oral	+	-	-	Regression of pulmonary metastases	9 + „	„	
Spindle-cell Sarcoma of Chest Wall										
64	44 M	X	„	+	-	-	No change in lesion of chest wall		Nil	

S=Surgery. X=Irradiation. * See case report in text.

while on intravenous therapy, but only eight patients (11%) required blood transfusion. Macrocytosis was always evident during treatment. Platelets were rarely depressed to below 100,000/c.mm. and only one case required fresh-blood transfusion, for melaena and haematuria due to thrombocytopenia. The white cells have been a most sensitive index of toxicity. The detailed haematological effects of this and other cytotoxic agents will be the subject of a separate communication.

Nausea and Vomiting.—This has occurred in approximately one-quarter of all patients, but in only one case was it severe enough to cause treatment to be abandoned: it was controlled with anti-emetics and sedatives.

Survival Time

Long-term results are not encouraging (Table I). Despite initial improvement most cases relapsed while on treatment. Only seven patients showed objective improvement for a period longer than six months; a further three were classified as obtaining subjective improvement over the same period.

Discussion

Cyclophosphamide seems to be of value in the management of advanced malignant disease. Of the 76 patients treated in this series, 23 showed a definite objective and measurable improvement and a further eight subjective improvement. The range of malignant conditions benefited by this drug is very similar to that reported by other workers using related compounds of the nitrogen mustard group. The encouraging short-term results reported here may be due in part to the relatively high dosages of the drug given, as judged by the degree of leucopenia produced.

Varying degrees of success have been reported by other workers using cyclophosphamide in a wide range

of malignant disease (Gross and Lambers, 1958; Snyman and Falkson, 1960; Korst *et al.*, 1960; Matthias *et al.*, 1960; Molin, 1961; Stoll and Matar, 1961).

Cyclophosphamide has certain advantages over many of the currently available cytotoxic drugs. Unlike mustine (HN2) injection presents no specific problems, for it is stable in aqueous solution and has no vesicant effect on tissue. Oral administration is effective and so allows maintenance therapy. It is felt that continued treatment has produced longer remissions than those reported by Stoll and Matar (1961) using single massive doses in advanced breast cancer.

The final method of action of cyclophosphamide is similar to other alkylating agents. Actively dividing cells in all tissues, particularly in the tumour and in the bone-marrow, are subject to damage. Radioactive studies by Bolt *et al.* (1961), using tritium-labelled cyclophosphamide, have shown that the highest concentration of the drug is in the primary tumour and its metastases.

A certain degree of peripheral leucopenia is expected and is used as an indication of adequate treatment. If excessive damage to the bone-marrow occurs, with depression of the circulating white cells and platelets, immediate withdrawal of the drug is nearly always followed by recovery of bone-marrow function within four to seven days, when treatment may be resumed. Such prompt haematological recovery is not seen after the use of other related drugs and allows patients to receive more effective dosages without the danger of marrow failure lasting many days. However, particular care should be taken when giving cyclophosphamide to patients who, prior to treatment, are known to have bone-marrow depression due to malignant infiltration of the marrow or to previous irradiation therapy.

Alopecia is a most distressing side-effect for the patient, and occurs more often than with other nitrogen mustards. It is our practice to warn all patients of this

FIG. 5.—Case 62. Chest radiograph of patient with sarcoma of breast (left) before (October 29, 1959) and (right) after (February 4, 1960) treatment. Note pulmonary secondary deposit and effusion on right side have completely resolved—although new lesion has developed on the opposite side.

possibility in advance, but it was never felt to contra-indicate treatment, as the hair regrows during maintenance therapy.

Nausea and vomiting may occur, but this depends on the dosage and susceptibility of the patient. The severity and incidence of this side-effect is, in our opinion, less than that seen using comparable doses of mustine (HN2) or thiotepea.

Cyclophosphamide has been used by other workers as a prophylactic measure in conjunction with surgery. Denk *et al.* (1961) report a series of 282 cases of carcinoma of the bronchus which have been treated chemotherapeutically for two years after radical operation, and claim that at 18 months the survival rate was 81% compared with 42% without the drug. This form of treatment has not been used in this series.

The long-term results are not encouraging in the present series despite continued treatment. Only two patients, both with carcinoma of the breast, responded for more than one year and only one of these remained symptom-free after 18 months.

Summary

A series of 76 cases of disseminated malignant disease have been treated with cyclophosphamide (a cyclic nitrogen mustard phosphamide ester). Twenty-three of these cases showed an objective response. Long-term results are not encouraging. Complications and side-effects are discussed. It is suggested that treatment with cyclophosphamide is worth while in patients with advanced malignant disease, although response is often short-lived.

We are grateful to Mr. Victor Riddell, who was the first person to draw our attention to the potentialities of cyclophosphamide. We are indebted to Dr. J. L. Stafford for much helpful advice, and to other members of the consultant staff of St. George's Hospital who have allowed their patients to be included in this series. We thank the photographic department of St. George's Hospital for the illustrations, and Dr. J. M. Simister, of Ward, Blenkinsop & Co. Ltd., for supplies of the drug. One of us (N. H. K.) acknowledges his gratitude to the British Empire Cancer Campaign for a full research grant during the tenure of which much of this work was carried out.

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"Science is rarely advanced by what is known in current jargon as a 'break-through.' Rather does our increasing knowledge depend on the activity of thousands of our colleagues throughout the world who add small points to what will eventually become a splendid picture, much in the way that the Pointillistes built up their extremely beautiful canvases." (Anniversary address to the Royal Society by Sir HOWARD FLOREY, P.R.S.)

HIGH-DOSE NITROGEN MUSTARD THERAPY WITH INTERMITTENT AORTIC OCCLUSION

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Nitrogen mustard (methyl-bis (β -chloroethyl) amine, HN2) is an alkylating agent widely used in the treatment of malignant disease (Rhoads, 1946). Alkylating agents are believed to interfere with tissue growth by reacting with the cellular nucleic acids (Zamenhof *et al.*, 1956; Stacey *et al.*, 1958). This effect is not tumour-specific, and the highest degree of inhibition appears to be achieved with tissues undergoing the most rapid replacement. Apart from tumour tissue, these include bone-marrow, lymph nodes, and intestinal epithelium.

HN2 produces cellular damage in these tissues which can readily be observed histologically as early as one day after administration (Sternberg *et al.*, 1958). Biological evidence of its cytotoxic effect *in vivo* can be obtained as early as 10 minutes after administration (Burchenal *et al.*, 1951). The kinetics of the affected cell type determine the timing of the clinical symptoms. Lymphocyte depression may become apparent within hours, intestinal disturbances—rarely at conventional doses—within days. Three weeks may elapse before the depression of the white-cell precursors is fully reflected as leucopenia in the peripheral blood. For all practical purposes, the effects of several doses of HN2 given within a short period of time appear to be cumulative for the proliferating tissues.

In addition, there are effects of HN2 which are not related to cell reproduction but concern the nervous system and produce symptoms immediately. While nausea and vomiting are often observed with conventional doses, fatal convulsions, like those occurring in cats after high doses (Sternberg *et al.*, 1958), have not been observed in man after systemic administration of tolerated mustard doses. There is no conclusive evidence that effects on the nervous system are cumulative if HN2 is administered in fractionated doses.

Clinically, the most important manifestation of mustard toxicity after systemic administration is bone-marrow depression. The dose which can be tolerated by the patient is the dose from which his bone-marrow can recover before fatal complications occur. Therefore attempts have been made to raise the concentration of