# CLINICAL EXPERIENCE WITH CYCLOPHOSPHAMIDE IN MALIGNANT DISEASE*

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WITH AN awareness of the temporary and often incomplete palliation afforded by nitrogen mustard and other well-known alkylating agents to patients suffering from malignant disease, from mid 1959 the newer nitrogen mustard derivative, cyclophosphamide, was used in selected cases. By October 1960, 67 patients, most of whom had advanced malignant disease, had been treated, and have since been followed up for a minimum period of six months.

The selection of patients was based on the clinical decision that an alkylating agent might be of benefit to the patient, and that further surgery or radiation if used alone would be less effective. The literature indicated that cyclophosphamide is less toxic than nitrogen mustard, and it seemed reasonable to try this drug in a number of cases in combination with radiation therapy to determine if there was any additive effect. It was agreed, when the study was begun, that if toxicity was high, or if the patient seemed to deteriorate rapidly, the drug would be withdrawn.

## *Review of the Literature*

Table I summarizes the results of published series in which definite figures for response and failure are recorded. Sometimes the figures quoted are difficult to interpret, and the reported result is classed as a "response" if the authors considered the drug useful. This obviously detracts from the value of the table but it does give a general picture of the numbers and types of cases that have been reported to date. The numbers of cases in each category are limited, and details of the pathological findings often are not described, so that the data regarding the response to the drug are not to be accepted uncritically.

At the present time there is a great need for some generally accepted scheme by which the response to an anticancer drug can be recorded. This subject is extremely complex, and it seems probable that separate criteria will be necessary for the evaluation of different types of neoplasms. The natural history of each is of the utmost importance and must be given due attention in the formulation of such criteria. This is particularly important in the lymphomas and leukemias, but this factor is less of a problem with the group of solid tumours.

Most authors list their own criteria, but these vary widely. For example, one author cites as "good response" complete objective and subjective remission for six months, while at the other extreme some workers consider objective remission to have occurred if any one physical sign diminishes. Another considers that a case cannot be evaluated unless there is some definite pathology which can be measured. These views are widely divergent and the application of them does not always give a clear indication of the usefulness of the drug.

In addition to the results quoted in the table, a single excellent result in a patient with chorionepithelioma is reported by Eufinger.[29] Simon[34] reports a series of patients with glioblastomas with 50% favourable results following treatment with cyclophosphamide, but in our opinion these were not followed up for an adequate period. Delmon[28] claims useful and objective responses in patients with carcinoma of the stomach, in contrast to the experience of other authors.

A survey of the dosage used by various authors shows wide variation both in the amount of drug given and the duration of treatment. For example, Coggins, Ravdin and Eisman[5, 27] administer the drug in one of two schedules: in the first regimen a single large intravenous dose, varying from 45 to 100 mg. per kg. of body weight, is given, with repetition of this same dose, or three-quarters of it, in about three weeks if the patient's general condition and blood counts permit. The other regimen used by these workers consists of high dosage repeated daily for six days, most patients receiving an average daily dose of 7.5 mg./kg. Several of these courses are given, depending on the tolerance of the patient and his blood-forming tissues. There is some indication that a higher proportion of responses occurs with these high-dose schedules than in other series. Other regimens reported consist of once-weekly or twice-weekly medication with a wide variation of dosages. However, in most of the series reported, the authors favour prolonged therapy, giving daily doses of approximately 3-4 mg./kg. The drug is usually stopped in the event of improvement, remission or toxicity, or when a predetermined cumulative dose has been reached. When a response is obtained, some workers prefer to continue with maintenance treatment at daily or weekly intervals, usually at a reduced dosage; on such maintenance therapy some extraordinarily high total doses have been given over long periods of time.

## *Administration and Dosage*

Because many of our patients could attend on an outpatient basis, a prolonged course was given at moderate dose level; treatment was started with an intravenous injection of 100 mg. of cyclophosphamide, followed by 200 mg. daily, irrespective of height and weight; this was equivalent to 3 to 4

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TABLE I.

| *Disease* | *Numbers responding over No. of cases treated* | *Total* | *% response* | *References* |
|---|---|---|---|---|
| RETICULOSES | | | | |
| Hodgkin's disease | 1/2 3/6 15/26 5/6 2/3 4/4 1/1 9/14 | | | 1, 2, 3, 6, 7, 11, 12, 12A |
| | 10/14 7/12 14/15 16/17 3/3 2/2 3/4 6/11 1/1 | 102/141 | 72% | 14, 16, 17, 18, 19, 21, 23, 24, 26 |
| Reticulum cell sarcoma | 1/1 4/4 3/5 1/2 0/1 1/1 2/2 1/1 | | | 1, 2, 3, 6, 11, 12, 12A, 14, |
| | 1/1 1/1 3/3 1/1 5/5 0/1 2/6 | 26/35 | 74% | 15, 18, 19, 21, 22, 23, 24 |
| Giant follicular lymphoblastoma | 0/1 2/2 1/1 | 3/4 | — | 2, 12, 18 |
| Lymphosarcoma | 3/4 6/14 4/7 1/2 2/5 5/5 1/1 2/3 | | | 2, 3, 6, 7, 8, 11, 12, 12A |
| | 1/1 2/2 2/3 7/7 1/1 4/6 3/6 | 44/67 | 66% | 16, 17, 18, 19, 21, 23, 24 |
| Malignant lymphoma (unspecified) | 9/13 5/7 1/1 1/2 | 16/23 | 70% | 5, 10, 14, 24 |
| Chronic lymphatic leukemia | 8/19 2/2 5/6 6/6 2/4 4/5 1/1 1/5 0/1 | 29/49 | 59% | 3, 11, 12, 12A, 16, 18, 21, 24, 25 |
| Chronic myeloid leukemia | 1/1 9/9 4/4 0/1 0/2 | 14/17 | 82% | 6, 11, 12, 12A, 24 |
| Subacute eosinophilic leukemia | 0/1 | 0/1 | — | 16 |
| Acute leukemia | 1/10 4/14 0/1 2/2 6 (C)/13 13 (C)/37 9 (A)/45 1/1 0/5 5/9 | 41/137 | 30% | 2, 3, 5, 7, 9, 13, 13, 19, 21, 15 |
| | C—children, A—adults, remainder unspecified | | | |
| Polycythemia rubra vera | 1/1 1/1 | 2/2 | — | 12, 18 |
| Multiple myeloma | 1/1 0/1 0/13 3/5 0/5 1/1 1/1 3/4 9/14 2/2 0/3 | 20/50 | 40% | 1, 2, 3, 6, 10, 11, 12A, 16, 18, 21, 24 |
| *Mycosis fungoides* | 1/1 0/1 | 1/2 | — | 2, 16 |
| CARCINOMAS | | | | |
| Tongue | 0/4 | 0/4 | — | 24 |
| Parotid | 1/1 | 1/1 | — | 6 |
| Larynx | 1/1 2/2 0/5 | 3/8 | — | 5, 10, 24 |
| Nasopharynx (epidermoid) | 2/2 | 2/2 | — | 10 |
| Tonsil | 1/1 | 1/1 | — | 1 |
| Lymphoepithelioma | 1/1 1/3 1/1 | 3/5 | — | 2, 24, 26 |
| Pharynx and larynx | 1/4 0/9 | 1/13 | 8% | 2, 6 |
| Thyroid | 0/1 0/2 | 0/3 | — | 5, 24 |
| Trachea | 0/1 | 0/1 | — | 1 |
| Lung | 10/16 1/6 3/6 2/9 2/5 3/4 0/1 0/1 0/3 3/30 0/1 | 24/82 | 29% | 1, 2, 3, 5, 6, 10, 16, 18, 19, 24, 26 |
| Esophagus | 0/1 0/4 0/1 | 0/6 | — | 6, 24, 26 |
| Stomach | 1/3 0/1 0/1 0/5 0/5 | 1/15 | 7% | 1, 3, 19, 24, 25 |
| Colon | 0/1 0/1 | 0/2 | — | 1, 19 |

TABLE I.—*Continued*

| *Disease* | *Numbers responding over No. of cases treated* | *Total* | *% response* | *References* |
|---|---|---|---|---|
| Carcinoid tumour | 0/1 | 0/1 | — | 24 |
| Rectum | 0/1 | 0/1 | — | 18 |
| Anus | 1/2 | 1/2 | — | 10 |
| "G.I. tract" | 0/11 2/16 | 2/27 | 7% | 2, 5 |
| Pancreas | 0/1 0/1 | 0/2 | — | 2, 3 |
| Hepatoma | 0/1 0/1 | 0/2 | — | 24, 26 |
| Adrenal | 0/1 0/1 | 0/2 | — | 6, 19 |
| Kidney carcinoma | 0/1 1/2 0/1 0/1 0/6 | 1/11 | 9% | 1, 2, 5, 19, 24 |
| Wilms' tumour | 0/1 0/2 0/1 | 0/4 | — | 19, 20, 24 |
| Renal pelvis | 1/1 | 1/1 | — | 26 |
| Bladder | 0/2 | 0/2 | — | 24 |
| Prostate | 0/1 0/1 2/8 | 2/10 | 20% | 5, 19, 24 |
| Testis (embryonal) | 1/2 1/1 | 2/3 | — | 16, 19 |
| (Unspecified) | 0/2 0/1 | 0/3 | — | 2, 5 |
| Ovary | 2/3 2/5 0/2 6/9 1/1 1/1 3/4 8/23 1/2 | 24/50 | 48% | 1, 2, 3, 5, 6, 10, 19, 24, 25 |
| Fallopian tube | 0/1 | 0/1 | — | 6 |
| Corpus uteri | 1/2 1/5 2/8 | 4/15 | 27% | 2, 5, 24 |
| Cervix uteri | 1/1 1/9 1/3 1/3 5/28 1/1 | 10/45 | 22% | 1, 2, 5, 6, 24, 26 |
| Vulva | 0/1 | 0/1 | — | 24 |
| Breast | 2/5 0/6 1/1 3/8 1/1 2/13 0/4 | 9/38 | 24% | 1, 2, 3, 5, 14, 24, 26 |
| Male breast | 0/1 | 0/1 | — | 5 |
| Skin | 0/1 | 0/1 | — | 26 |
| Sweat gland | 0/1 | 0/1 | — | 24 |
| Melanoma | 0/1 3/8 1/2 0/1 1/3 0/3 1/2 0/1 1/5 1/1 | 8/27 | 30% | 2, 5, 10, 11, 12, 14, 16, 19, 24, 25 |
| Carcinomatosis (primary unknown) | 1/3 2/4 1/3 4/9 0/2 0/2 0/5 2/2 | 10/30 | 33% | 1, 2, 5, 11, 19, 21, 24, 26 |
| Effusions | 2/5 3/7 | 5/12 | 42% | 4, 24 |
| SARCOMAS | | | | |
| Osteogenic sarcoma | 1/3 0/1 | 1/4 | — | 20, 24 |
| Ewing's tumour | 1/1 0/1 1/1 | 2/3 | — | 16, 20, 25 |
| Fibrosarcoma | 1/2 | 1/2 | — | 2 |

TABLE I.—*Concluded*

| *Disease* | *Numbers responding over No. of cases treated* | *Total* | *% response* | *References* |
|---|---|---|---|---|
| Liposarcoma | 0/1 1/1 | 1/2 | — | 2, 18 |
| Myxosarcoma | 0/1 | 0/1 | — | 25 |
| Rhabdomyosarcoma | 1/2 1/1 0/1 3/4 (children) | 5/8 | — | 2, 7, 16, 20 |
| Leiomyosarcoma | 0/3 | 0/3 | — | 24 |
| Synovioma | 0/1 | 0/1 | — | 24 |
| Sarcoma (undifferentiated) | 0/1 0/1 0/1 0/1 | 0/4 | — | 2, 16, 24, 26 |
| Neurofibrosarcoma | 0/1 | 0/1 | — | 5 |
| Schwannoma | 0/1 | 0/1 | — | 16 |
| Kaposi's sarcoma | 0/1 | 0/1 | — | 24 |
| MISCELLANEOUS | | | | |
| Mesothelioma | 0/2 | 0/2 | — | 24 |
| Pleura, unspecified | 1/2 | 1/2 | — | 1 |
| Teratoma | 1/2 0/1 | 1/3 | — | 20, 24 |
| Neuroblastoma | 0/3 1/1 | 1/4 | — | 20, 25 |
| Ependymoma | 0/1 | 0/1 | — | 24 |

mg./kg. In a few patients the dose was cautiously raised to 400 mg. daily, but nausea was more troublesome at this level and in a number of cases the dose had to be reduced again.

At first the treatment was given for five days each week but it was soon recognized that this rate of administration, 1 g. weekly, was too low and time-consuming. Later, treatment was given six or seven days each week directed toward the administration of a minimum of 5 g. of cyclophosphamide in four weeks wherever possible, and continuing to higher dosage if this was well tolerated and a response to the drug was obtained. After one to three weeks of intravenous injections many patients, particularly those who went home, continued with oral cyclophosphamide at the dosage of 200 mg. daily (4 x 50 mg. tablets).

During and after treatment, all patients were examined frequently, blood counts were done, and where possible the size of tumour masses was measured and serial radiographs were taken.

### *Side Effects*

From the patient's point of view the only important side effects are nausea and alopecia. The clinician's main concern is depression of the bone marrow. Other side effects occur, but they are infrequent and depend largely on the dosage used.

Some nausea occurred in 60% of our patients and was often evident within the first week of treatment. In almost every instance its severity could be lessened with the commonly used antiemetic drugs. Vomiting occurred at some time in 22% of patients. Other gastrointestinal effects were uncommon: two patients had diarrhea; one had hematemesis from a gastric ulcer which may be considered coincidental; and four patients complained of a foul taste in the mouth after intravenous administration of the drug, coming on a few minutes after the injection and lasting for several hours.

The extent of the disease bears a relationship to the incidence of nausea and vomiting; those patients with localized disease, who were in fairly good health, usually took the drug well with little upset.

Alopecia of some degree occurred in nine of 42 men (21%) and in nine of 25 women (36%). The incidence in men is higher than was expected and may be due to the fact that leading questions were asked concerning this complication. The total dosage is important: if patients who received less than 3 g. are excluded, the overall rate of alopecia in men and women combined rises to 36%. Hair loss, usually evident as an excessive accumulation on the comb, was noticed some two to three weeks after the drug had been started. Hair loss usually

persisted during the period of administration and for a short time thereafter; pubic and axillary hair was unaffected.

Hair often began to grow again during the period of oral maintenance therapy. Complete alopecia occurred in only four cases. Most of our patients suffered a diffuse thinning of scalp hair; patchy hair loss was rather uncommon, although it has been reported in 50% of one reported series. Regrowth was usually complete in three months, at least as far as hair thickness was concerned, and most patients were satisfied with their new head of hair. In one woman with straight greying hair, regrowth of darker and more curly hair occurred, to her pleasure.

No other alkylating agent currently in use produces alopecia. From a survey of the literature the occurrence of alopecia seems related to the total dosage and the time over which cyclophosphamide is administered. Coggins, Ravdin and Eisman,[5, 27] workers who employed the highest dosage schedule, reported an alopecia rate of 90% which was equally distributed between the sexes. Bergsagel and Levin[2] report that 27% of their patients had hair loss. Foye *et al.*[10, 10a] noted patchy alopecia in six of 25 patients (25%), and Matthias, Misiewicz and Bodley Scott[18] give evidence of alopecia in six in 45 cases (13%). Papac *et al.*[19] describe 10 patients in 31 (32%) who are equally divided between those with patchy and those with diffuse hair loss. Haar *et al.*[12] record five in 20 (25%), and Shnider *et al.*[24] 15 in 47 (32%) of those treated by oral administration on various regimens and an incidence of 19% of those treated by intravenous injection. Hoogstraten *et al.*[13] report that 15% of patients receiving over 4 g. had this complication. Regrowth of hair seems to be the rule.

In four patients throbbing headaches were a prominent symptom; these subsided when the drug was discontinued. A sense of tiredness was a common symptom but was seldom volunteered by the patient. It is hard to dissociate this symptom from the weariness that the underlying disease may cause.

Three patients developed herpes zoster: one patient had lymphosarcoma, the other two had Hodgkin's disease. In both cases of Hodgkin's disease the herpes was extensive, but need not be ascribed to cyclophosphamide because it occurs frequently in the natural evolution of this disease.

When radiotherapy was combined with drug treatment there may have been a slight increase in nausea and gastrointestinal disturbances, but in no case was this symptom excessive. These two methods of treatment can be combined conveniently.

Thrombophlebitis at the site of injection did not occur; it was usually possible to complete the whole course of intravenous injections through one vein.

Those authors who employ a high dosage in a short time have recorded such side effects as dizziness, blurring of vision and sterile chemical cystitis. These symptoms were not observed in our cases or in other series where a prolonged period of treatment was used. Haas[30] has reported disturbance of wound healing when cyclophosphamide was given at the time of laryngectomy. This is a nonspecific complication which has been reported with the use of other alkylating agents in association with major surgery.

The effect of this agent on the hematopoietic system is described in detail in other reports, especially those of Petrides and Moncke[32, 33] and Nissen-Meyer and Hoest.[31] This aspect of the subject will not be dealt with here. Most of our patients had previous chemical or radiation therapy, which complicated the hematological picture.

Of all the patients treated, the white blood count fell to less than 2000 per c.mm. in 19 cases. These findings confirm the work of others who found that cyclophosphamide depresses the platelet count much less than nitrogen mustard and other alkylating agents. The platelet count fell to below 100,000 per c.mm. in only three cases; and the count returned to normal levels rapidly when the drug was discontinued.

Cyclophosphamide is the safest alkylating agent available at the present time. The white blood cell count can be reduced to 1250 without danger, provided the platelets do not fall significantly below 100,000 per c.mm. The degree of white cell and platelet depression is related to the extent of bone marrow involvement, liver disease[2] and previous chemical or radiation treatment.

## RESULTS

Table II shows the response in 67 patients with advanced malignant disease treated with cyclophosphamide at the Edmonton Cancer Clinic. Histological proof of diagnosis was not obtained in one patient; and no patient was lost to follow-up. A "good result" implies relief of the principal symptoms and regression, or at least arrest, of previously progressing lesions, for a period as long as that which occurs with present methods of treatment. Several favourable responses are classified as "partial response", where new lesions appeared either during or after treatment although regression of the main mass or masses was observed. Minor degrees of improvement have been ignored.

### *Hodgkin's Disease*

Seven patients with generalized Hodgkin's disease were treated, three males and four females. Six had been diagnosed at least three years previously and had multiple treatments either by radiation or alkylating agents in the past. This reference

TABLE II.

| Disease | Sex | Age | Total dose (G.) | Evaluation of response: Good | Partial | Uncertain | No effect | Inadequate dose | Survival (weeks) | Living or dead on April 1/61 | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hodgkin's Disease | M | 56 | 1.2 | | | | | 1 | 2 | D | Total duration of disease—18 months. Moribund when treated. |
| | M | 27 | 4.7 | | | | 1 | | 13 | D | Total duration of disease—4 years. |
| | M | 55 | 5.0 | | 1 | | | | 24 | D | Prior and concurrent ACTH. Total duration—4 yrs. |
| | F | 41 | 2.0 | | 1 | | | | 45 | D | Subjective improvement. Total duration—5 years. |
| | F | 15 | 1.3 | 1 | | | | | 58 | L | Previous duration 3 years with many treatments. Seemed terminal when cyclophosphamide started. |
| | F | 18 | 1.8+R | + | | | | | 58 | L | Previous history—3 years. |
| | F | 35 | 2.3 | | 1 | | | | 78 | L | New nodes developed during treatment, but general condition greatly improved—previous duration—5 years. |
| 7 cases | | | | 2 | 3 | 0 | 1 | 1 | | 3L | |
| Lymphosarcoma | M | 27 | 5.0 | | 1 | | | | 20 | D | Axillary nodes resolved dramatically but disease progressed generally. |
| | M | 80 | 0.7+R | | | | | 1 | 33 | L | Good response to radiation. |
| | M | 54 | 2.7+R | | | | | 1 | 10 | D | Total duration 5 years with repeated radiation. Far advanced when treated with cyclophosphamide. |
| 3 cases | | | | 0 | 1 | 0 | 0 | 2 | | 1L | |
| Reticulum cell sarcoma | F | 62 | 2.7+R | | | | | 1 | 6 | D | Primary probably stomach. Radiosensitive, but recurred rapidly. |
| | F | 57 | 6.1 | | | | 1 | | 15 | D | ?Primary in sternum. Radiosensitive. New lesions developed during treatment with cyclophosphamide. |
| | M | 41 | 8.0 | | 1 | | | | 26 | D | Primary ischiorectal fossa 8 years previously. On cyclophosphamide some lesions regressed, others advanced. |
| | M | 56 | 9.4 | | 1 | | | | 14 | D | Good remission on I.V. cyclophosphamide and cortisone, but relapsed on oral cyclophosphamide. |
| 4 cases | | | | 0 | 2 | 0 | 1 | 1 | | 0L | |
| Multiple myeloma | F | 46 | 8.3 | 1 | | | | | 53 | L | Good subjective response. Lesions stationary radiologically. |
| | M | 57 | 9.0 | 1 | | | | | 37 | D | Recalcification of bone lesions. Rapid terminal deterioration with liver enlargement (amyloid). |
| | M | 88 | 7.0+R Oral | + | | | | | 32 | D | Striking result. Almost moribund at start. |
| | M | 71 | 15.7 | 1 | | | | | 77 | L | Pain relieved. Lesions stationary. |
| | M | 61 | 6.0 | | | | 1 | | 24 | D | Downhill course unaffected by cyclophosphamide and by urethane. |
| | F | 38 | 5.7+R | 1 | | | | | 59 | L | 5-month remission including unirradiated areas. |
| | M | 59 | 2.9+R | | | | | 1 | 17 | D | Hemiplegic. No improvement. |
| 7 cases | | | | 5 | 0 | 0 | 1 | 1 | | 3L | |
| Ewing's sarcoma | M | 14 | 10.8+R | 1 | | | | | 44 | D | Widespread metastases, four courses of treatment. |
| | M | 9 | 2.5+R | | | 1 | | | 29 | L | Primary treated (femur) with full radiation. Impossible to assess effect of cyclophosphamide. |
| Fibrosarcoma | M | 66 | 2.9 | | | | | 1 | 15 | D | Primary quadriceps. Continued growth of lung metastases. |
| | M | 19 | 4.7 | | | | 1 | | 23 | D | Primary biceps. Lung metastases. |
| Leiomyosarcoma | F | 48 | 3.8+R | | | | 1 | | 18 | D | Primary probably ovary. Advanced. |
| | F | 53 | 4.8 | | | | 1 | | 20 | D | Primary stomach. Radioresistant. |
| Sarcoma (undifferentiated) | M | 12 | 6.7 | | 1 | | | | 16 | D | Regression of primary. No change in lung metastases. |
| Lymphoepithelioma of pharynx | M | 68 | 5.2+R | | | | 1 | | 26 | D | Chinese. Temporary response to radiation. |
| | M | 37 | 5.5 | | | | 1 | | 28 | D | Total duration 3 years with radiation. New lesions developed during treatment. |
| Tongue | M | 71 | 2.3 | | | | 1 | | 8 | D | Very advanced, squamous cell grade III. |
| Adenocarcinoma of stomach | M | 56 | 7.5 (Oral) | | | | 1 | | 13 | D | Widespread secondaries. |
| | M | 72 | 7.1+R | | | + | | | 38 | L | Good result in conjunction with radiation 3500 rad. |
| | M | 60 | 5.2+R | | | | 1 | | 9 | D | Liver metastases. |
| 3 cases | | | | 0 | 0 | 1 | 2 | 0 | | 1L | |
| Adenocarcinoma of large bowel | F | 33 | 1.6 | | | | | 1 | 9 | D | Carcinomatosis peritonei. |
| | M | 73 | 2.1+R | | | + | | | 26 | D | Cecum. Probably better palliation than radiation alone. |
| | M | 50 | 11.0+R | | | + | | | 53 | L | Cecum. 3 separate courses. Probable growth restraint. |
| | F | 65 | 4.5+R | | | + | | | 38 | L | Colon. Probably better than radiation alone. |
| 4 cases | | | | 0 | 0 | 3 | 0 | 1 | | 2L | |
| Anaplastic carcinomatosis of the omentum | F | 59 | 6.0 | | | 1 | | | 14 | D | Subjective improvement. |
| Ovary | F | 46 | 7.7 | 1 | | | | | 57 | L | Abdominal carcinomatosis, undifferentiated. Subsequent radiation to pelvis only. |
| | F | 44 | 3.6+R | | | + | | | 34 | L | Extensive serous cystadenocarcinoma. 3600 rad; impossible to assess separately. Excellent response. |
| | F | 34 | 6.0 | | | | 1 | | 21 | D | Papillary cystadenocarcinoma. |
| | F | 62 | 1.1+R | | | | | 1 | 13 | D | Treatment poorly tolerated. |
| 4 cases | | | | 1 | 0 | 1 | 1 | 1 | | 2L | |

TABLE II.—*Continued*

| | | | | *Evaluation of response* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Disease* | *Sex* | *Age* | *Total dose (G.)* | *Good* | *Partial* | *Uncertain* | *No effect* | *Inadequate dose* | *Survival (weeks)* | *Living or dead on April 1/61* | *Remarks* |
| Testis (embryonal cell carcinoma) | M | 49 | 4.3+R | | | | 1 | | 16 | D | Radioresistant. |
| | M | 38 | 6.1+R | | | | 1 | | 22 | D | Slight response to radiation. |
| | M | 23 | 1.2+R | | | | | 1 | 11 | D | Radioresistant. |
| | M | 32 | 5.8 | | | | 1 | | 6 | D | Previous good response to radiation, very sensitive. |
| 4 cases | | | | 0 | 0 | 0 | 3 | 1 | | 0L | |
| Hypernephroma | M | 40 | 3.7+R | | | | 1 | | 27 | D | Bone and lung metastases progressed. |
| | F | 63 | 3.5+R | | + | | | | 33 | L | Response to combination; previously radioresistant. Lung metastases unaffected. |
| | F | 50 | 8.0+R | | + | | | | 15 | D | Subcutaneous metastases responded better to combination than to either agent separately. |
| | M | 74 | 5.9+R | + | | | | | 23 | D | Very large masses responded. Radiation 4400 rad in 8 weeks. |
| | F | 78 | 2.6+R | | | | | 1 | 14 | D | Radiation dose small. |
| | F | 64 | 3.1+R | | | | 1 | | 19 | D | Primary responded to 3500 rad, but lung metastases appeared. |
| 6 cases | | | | 1 | 2 | 0 | 2 | 1 | | 1L | |
| Bladder | F | 36 | 5.0 | | | | 1 | | 34 | L | Lung metastases progressed. |
| Cervix uteri | F | 45 | 3.0 | | | | 1 | | 17 | D | Radioresistant, stage III. |
| Corpus uteri | F | 35 | 4.5+R | | | + | | | 23 | D | Growth restraint in conjunction with radiation and progesterone. |
| Carcinoma of lung | M | 64 | 7.6+R | | | + | | | 12 | D | Excellent regression but died of mycotic pneumonia. Squamous. |
| | M | 60 | 8.5 | | | | 1 | | 15 | D | Anaplastic; radiosensitive. |
| | M | 50 | 13.5 | | 1 | | | | 21 | D | Dramatic resolution of skin nodules, but other lesions progressed. Anaplastic. |
| | M | 47 | 4.2 | | | | 1 | | 9 | D | Oat cell. Skin nodules and liver metastases. |
| | M | 44 | 2.1 | | | | | 1 | 26 | D | Epidermoid. Treatment interrupted by hematemesis. |
| | M | 67 | 3.0+R | | | | 1 | | 4 | D | Epidermoid. Rapid decline. |
| | M | 70 | 1.0 | | | | | 1 | 11 | D | Epidermoid. |
| | M | 71 | 12.0 | | | | 1 | | 24 | D | Epidermoid. Lesions progressed. |
| | F | 57 | 4.8 | 1 | | | | | 13 | D | Epidermoid. Cerebral metastases. Seven weeks' remission. |
| 9 cases | | | | 1 | 1 | 1 | 4 | 2 | | 0L | |
| Mesothelioma of pleura | M | 50 | 0.6 | | | | | 1 | 2 | D | Moribund. |
| Skin | M | 75 | 4.0 | | | | 1 | | 14 | D | Inguinal nodes secondary to buttock. |

TOTAL
67 cases (30 with radiation) "Good" 11; "Partial" 11; "Uncertain" 9; "No effect" 23; "Inadequate dose" 13; 15 "Living"

EXPLANATORY NOTES:

1. In the column headed "Total Dose," the symbol "+R" is added when radiation therapy was given concurrently. Small fields to local deposits irrelevant to the general course of the disease have been ignored in a few instances.
2. In "Evaluation of Response" the symbol "+" indicates a favourable response in conjunction with radiation. These are only entered as "good" or "partial" if this was definitely better than could be expected by the radiation dose given. Otherwise such cases are entered as "uncertain" since the benefit could not definitely be ascribed to the drug.
3. A total dose of cyclophosphamide less than 3.0 g. is entered as "inadequate dose" unless there was a favourable response.
4. We have ignored minor degrees of subjective improvement or very temporary response.
5. The minimum follow-up period is 6 months.

to the natural history of the disease is important because patients who survived for this length of time must be those with the less malignant variants of the disease. One male, almost moribund when treatment was started, died two weeks later; another, who was first diagnosed four years previously, showed no worthwhile response; our third male patient received little benefit except for slight symptomatic improvement and reduction in fever.

The female patients had a much better response; three out of four are still alive and in moderately good health. The patient who died had extensive disease accompanied by persistent pruritus which had made her life miserable for three years; this symptom was relieved considerably by treatment with cyclophosphamide. The three patients who are living have had remissions lasting longer than one year. All had concurrent radiotherapy to mediastinal masses. Regression occurred in one patient who previously had received radiation to the mediastinum with little evidence of response. Each of these patients has since received an occasional single treatment with x-ray to painful areas, but this cannot account for their general return of well-being; one patient previously bedridden is now able to walk.

The results reported in the literature are encouraging. Although it is not possible to separate with certainty subjective and objective responses, in a fairly representative group 55 of 92 cases (60%) showed objective response and worthwhile effect. If subjective criteria are included, a much higher

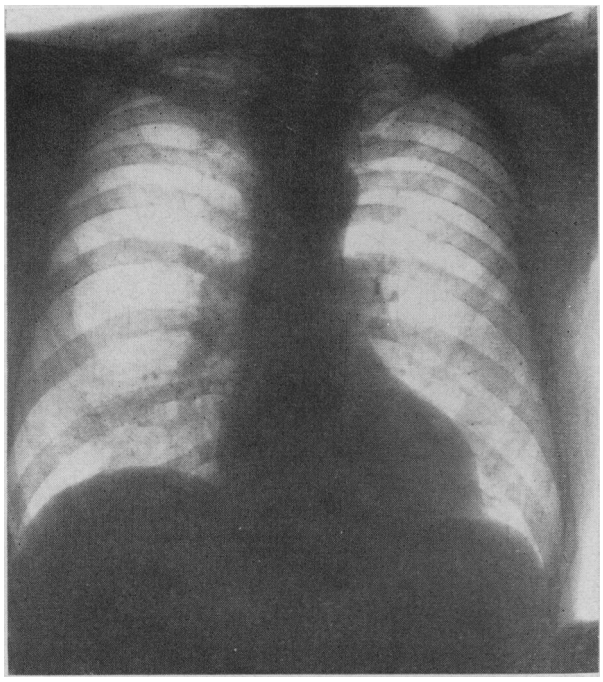

Fig. 1a

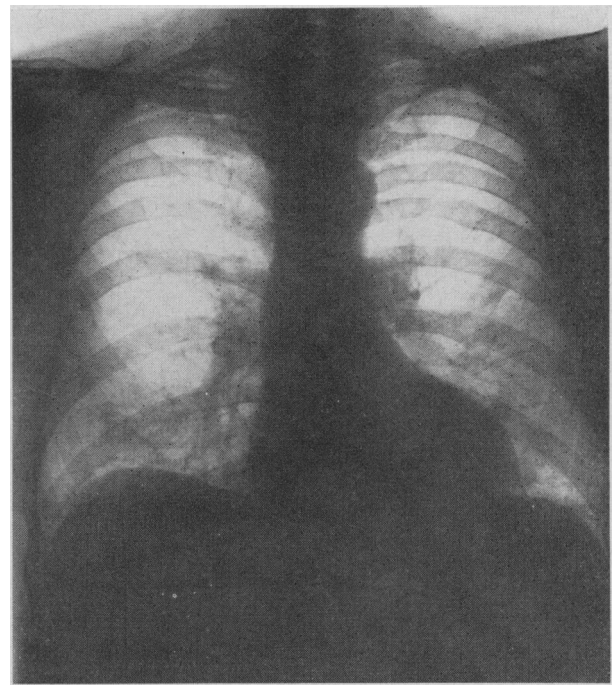

Fig. 1b

Fig. 1a.—Multiple myeloma. Male aged 57. Chest radiographs of December 14, 1959, before treatment. Fig. 1b.—February 24, 1960, after treatment with cyclophosphamide. Note particularly recalcification of lesions in right 5th rib and left 7th rib.

percentage of patients obtain benefit. Matthias, Misiewicz and Scott[18] report a favourable objective response in 65% and subjective improvement in 88%.

*Lymphosarcoma*

There were three cases of lymphosarcoma in this series. One elderly patient had received an inadequate dosage, but as he showed an excellent response to radiation, cyclophosphamide was discontinued. The second patient had extensive disease which was completely unaffected by the drug. The third had widespread disease but had reduction in the size of enlarged axillary lymph nodes although the disease as a whole progressed. The literature records a satisfactory objective response in about 55% of 36 collected cases of lymphosarcoma. The duration of remission is usually not given.

*Reticulum Cell Sarcoma*

Four patients with this disease were treated, but no worthwhile result was obtained. This disease pursues a most varied natural history. Localized tumour masses can often be controlled by radiation, but in our experience generalized involvement is rarely amenable to chemotherapy, and radiaion therapy in such cases produces little more than transient palliation.

The details of the cases of reticulum cell sarcoma treated are listed in Table II. Two patients receiving 8.0 and 9.4 g. respectively had slight improvement but the treatment was of little real value.

A survey of published cases showed that favourable response was described in 74%; details of the extent of the disease and the duration of the therapeutic result were generally not stated.

*Multiple Myeloma*

Seven patients with multiple myeloma were treated, and in most of these cyclophosphamide was the first anticancer drug to be given. One patient had a prolonged course of urethane previously without effect.

Five of the seven patients are classified as having "good" results. All of these had marked symptomatic improvement and although they had concurrent radiation therapy to certain areas, relief of pain was also observed in unirradiated areas. Three of these patients are living one year or more from the beginning of treatment; they have not had any evidence of relapse. Two of the "good" cases died, at 31 and 36 weeks respectively, one at age 89. Both of these patients died of the disease, but had had a definite remission which was ascribed mainly to cyclophosphamide.

In three of the patients with "good" response, prednisone in doses up to 15 mg. per day was given to maintain the white blood count. This was stopped as soon as the leukocyte count was satisfactory; discontinuing prednisone did not seem to result in early relapse. One patient had definite radiological evidence of recalcification of a number of lesions in ribs and elsewhere. This is illustrated in Fig. 1.

The results reported in the literature are not quite so encouraging as these, although the overall

response rate of 40% is impressive in a disease for which no satisfactory systemic therapy is known. A few treated cases in the literature have shown changes towards normal in the electrophoretic pattern,[16, 32] but most workers rely on the patient's subjective response. Spontaneous reduction in pain and a temporary arrest of the disease occasionally occurs and may be difficult to distinguish from the effects of therapy.

A series of 13 cases in whom no detectable response was obtained[3] were treated with oral cyclophosphamide only. The only other series of comparable size (Matthias, Misiewicz and Scott) showed nine patients responding out of 14 treated with intravenous injections of the drug. These authors reported a higher incidence of leukopenia during the treatment of this disease with cyclophosphamide than in other reticuloses so treated; this is in line with our experience.

*Ewing's Sarcoma*

Two patients with Ewing's sarcoma were treated with cyclophosphamide.

The first was a boy of 14 who had an amputation above the knee for Ewing's sarcoma of the right tibia in May 1958. He was well until January 1959, when metastases in the lungs and pelvis became apparent. From then until August 1959, he had many courses of radiotherapy to bone and soft tissue metastases; there was excellent local response, including improvement in lung metastases in the one half of the chest treated. In October 1959 the boy was treated with cyclophosphamide, in conjunction with prednisone, 15 mg. daily, because he had marked marrow depression from his disease and from previous therapy. A total of 3.6 g. of cyclophosphamide was given in three weeks; marked subjective improvement occurred and there was slight reduction in the measurable lesions. Further courses of cyclophosphamide were given because of an exacerbation of symptoms: in December 1959, 1.4 g.; in January and February 1960, 3.8 g.; and in May 1960, 2.0 g. On each occasion there was subjective benefit and slight objective response of the lung lesions. Supportive treatment with local radiation and blood transfusions was also given but the main effect was definitely attributable to cyclophosphamide. This patient also had one course of nitrogen mustard without apparent benefit. He died in August 1960, 44 weeks after the first course of cyclophosphamide.

In the light of this experience, the next patient with Ewing's sarcoma was given cyclophosphamide and a full course of radiotherapy as primary treatment. The combination was well tolerated and the patient is well without recurrence seven months later.

Three similar cases are reported in the literature; two responded to treatment with this agent.

*Soft Tissue Sarcoma*

Five patients were treated for soft tissue sarcomas. Two had primary fibrosarcoma of the extremities, with intrathoracic metastases; in these no useful result was obtained. Two patients had leiomyosarcoma, one originating in the stomach, the other from the right ovary; again, no useful effect was observed.

The fifth patient was a boy aged 12 who had an extensive undifferentiated sarcoma of the forearm, an enlarged liver and bilateral pulmonary metastases. Treatment with cyclophosphamide had a dramatic effect; his general well-being improved greatly, and the contour of the forearm returned to normal. Despite this encouraging initial response, the size of the liver did not change and the pulmonary lesions continued to increase. Eight weeks later he began to fail and he died 16 weeks after the first treatment.

*Lymphoepithelioma*

Two patients with recurrent lymphoepithelioma were treated, with no appreciable result.

*Cancer of Tongue*

One very elderly patient with extensive carcinoma of the tongue received both cyclophosphamide and cobalt beam therapy, without benefit.

*Stomach*

Three patients with adenocarcinoma of stomach were treated with cyclophosphamide. The first two had widespread abdominal deposits, one with definite liver metastases; despite dosages of 7.5 and 5.7 g. respectively no worthwhile result was noted. The third patient one year after gastrectomy developed a large metastatic mass in the rectovesical pouch with bladder invasion and hematuria. Treatment with cyclophosphamide and x-radiation gave excellent palliation; he had complete symptomatic relief for six months, after which local bleeding recurred.

Apart from Delmon's paper,[28] a survey of the literature records only one satisfactory response in 15 cases of carcinoma of the stomach.

*Large Bowel*

Three of our four patients with carcinoma of the large bowel were treated with cyclophosphamide in combination with local radiation; two are alive, with residual disease, at 9 and 12 months respectively. The third patient survived six months after having had good palliation. Because radiation was given only to the most prominent masses in the abdomen, we feel that the arrest of disease in the two patients still alive is largely attributable to cyclophosphamide therapy. The fourth patient did not respond, but had inadequate dosage of cyclophosphamide.

A fifth patient, not definitely diagnosed as having cancer of the large bowel but with widespread abdominal carcinomatosis, primary site unknown, is included here. He had subjective improvement with relief of pain with a dosage of 6 g. of cyclophosphamide; the remission lasted three months. Only two cases of this common disease are reported in the literature. No response followed treatment with cyclophosphamide.

*Carcinoma of Ovary*

Four patients with ovarian carcinoma were treated, with encouraging results. The first patient had extensive undifferentiated carcinoma with ascites, pain and vaginal bleeding. A dosage of 7.75 g. was given, with dramatic improvement in the patient's general well-being and shrinkage of tumour masses. In view of this excellent response, radiation therapy was given for the residual pelvic disease; it was tolerated well and the patient is free of symptoms more than one year later.

The second patient had a serous cystadenocarcinoma with extensive disease, extreme ascites and anemia. Large field radiotherapy was given over most of the abdomen in a tumour dose of 3600 rad in four weeks, combined with 3.6 g. of cyclophosphamide. The dose of x-radiation was high but it was well tolerated. No definite response was noted during the course of treatment. Immediately after treatment abdominal paracentesis was done on two occasions to remove accumulated ascite fluid. It has not accumulated again to date, eight months later.

The third patient, with papillary cystadenocarcinoma, showed no response to 6 g. of cyclophosphamide and died 21 weeks later. Our fourth patient had extensive disease and was not able to tolerate an adequate dosage.

The vagaries of ovarian cancer are many, and to obtain acceptable statistics in this disease a large series of patients is required. Reports of the use of cyclophosphamide in the literature show that 24 patients of 50 (48%) so treated had a satisfactory response. Cyclophosphamide should be used in the postoperative treatment of those patients in whom there is residual disease in the pelvis; the use of this drug should be combined with local radiation wherever possible.

*Malignant Tumours of the Testis*

Four patients with metastatic embryonal cell carcinoma of the testes were treated with cyclophosphamide, although one had inadequate dosage. All of these patients had pulmonary lesions and none of them responded. Radiotherapy had been given previously in two; one of them responded to this therapy, the other did not.

Of the six cases described in the literature two patients had a satisfactory response and both had embryonal cell carcinoma.

*Hypernephroma*

Six patients were treated because of hypernephroma, four females and two males. The first male patient had extensive local and pulmonary disease; he was treated with cyclophosphamide alone, without obvious effect. The second man had extensive stony-hard deposits throughout the whole abdomen. Palliative radiation therapy was given with relief of pain, and because of this response a second course of radiation was given combined with cyclophosphamide. During this second course of treatment 5.9 g. of cyclophosphamide was administered with symptomatic improvement and regression of tumour. It is difficult to be certain but there seems to have been some additive effect of the two therapeutic agents.

Our first female patient had inoperable local disease with extensive pulmonary involvement. However, the main sign was the periodic seeding of subcutaneous deposits; if these were left alone they tended to grow into large masses. Eight grams of cyclophosphamide was given over a long period, and regression of some of these masses was observed but they never disappeared completely; new masses appeared towards the end of the period of cyclophosphamide therapy. There were many subcutaneous masses of varying size; it was possible to leave some to be treated by cyclophosphamide alone, and to give additional x-ray therapy to others of comparable size. Those treated with additional radiation therapy either disappeared or absorbed to a greater extent. The pulmonary lesions were completely unaffected by the drug and even progressed.

In one of the three remaining patients some additive effect of radiation therapy and cyclophosphamide may have been evident. The tumour was locally recurrent and was previously radioresistant. Radiotherapy in the amount of 3000 rads combined with 3.5 g. of cyclophosphamide was given over a period of three weeks; the relief of pain which resulted lasted for three months.

It is hazardous to draw conclusions from six cases. Any effect obtained by radiation or cyclophosphamide was temporary, at best, but it seemed that in three of these six cases the addition of cyclophosphamide was of benefit. Hypernephroma is essentially a radioresistant lesion, especially when the volume of tumour is large. There was sufficient response in these three cases to warrant further trial of this agent in combination with radiation therapy in extensive disease. Pulmonary involvement is completely unaffected by cyclophosphamide alone.

A search of the literature is unrewarding. One case of hypernephroma out of 11 treated with this drug showed a beneficial response.

*Malignant Tumours of the Bladder*

One patient with cancer of the bladder, local pelvic disease and pulmonary involvement was

treated with a dose of 5 g. of cyclophosphamide, without demonstrable effect.

*Carcinoma of Cervix and Corpus Uteri*

One patient with squamous cancer of cervix, in an advanced stage and completely insensitive to radiation, was given 3 g. of cyclophosphamide without benefit. One patient with adenocarcinoma of the endometrium with widespread abdominal disease was treated with cyclophosphamide and 17-alpha-hydroxyprogesterone caproate (Delalutin), again with no useful result; some degree of palliation was obtained later by radiotherapy.

*Lung*

Nine patients with cancer of the lung and metastases were treated with this drug. All but one had had radiotherapy; four had had a thoracotomy and one a craniotomy. Histological studies showed that the tumour was an epidermoid carcinoma in six, and an anaplastic or oat cell carcinoma in three.

The therapeutic response was classified as "good" in a woman 57 years of age whose principal signs and symptoms at the time of treatment were due to intracranial metastasis from a primary epidermoid tumour of the lung. After two short-lasting responses to radiation she was treated with cyclophosphamide; in spite of the presence of liver metastases she had a remission which lasted for seven weeks before further deterioration occurred.

One patient with inoperable disease is classified in the "partial response" group because of striking and complete disappearance of ten skin nodules, one of which was proved to be carcinomatous by biopsy. However, in this patient, bone pain was not relieved and new lesions developed in the adrenals 13 weeks later, while the patient was still taking oral cyclophosphamide.

The remaining seven cases are regarded as treatment failures, with the possible exception of one patient in whom a very large epidermoid carcinoma of the lung, previously untreated, disappeared completely with cyclophosphamide in conjunction with x-ray therapy, a tumour dose of 3000 rad being given in three weeks. The patient died 12 weeks later, apparently from a mycotic pneumonia.

The results quoted in the literature show only occasional "good" responses, with the exception of the series reported by Aronovitch, Meakins and Groszman,[1] in which 10 of 15 patients with epidermoid carcinoma responded satisfactorily to cyclophosphamide, but no response was observed in one case of adenocarcinoma in this series. These authors particularly mention relief of pain due to bone metastases; we failed to obtain this result in our series with a similar dosage schedule. In the literature 24 of the 82 patients treated with cyclophosphamide showed some response, a rate of 29%.

*Mesothelioma of Pleura*

One patient with pleural mesothelioma was treated; he was moribund from the outset of treatment and died one week later. Two cases of this lesion are reported in the literature; a beneficial result from cyclophosphamide therapy was not observed in either of them.

*Skin Cancer*

One patient with enlarged inguinal nodes, secondary to squamous cancer of the skin of the buttock, was treated with cyclophosphamide without benefit.

## DISCUSSION

The widely varying dosage schedules testify to the safety of cyclophosphamide. The spectrum of cytotoxic action parallels that of nitrogen mustard with some exceptions; in our view the principal useful feature of this agent is its lesser toxicity, both clinical and hematological. Remissions are as long as those obtained with the parent compound, and in some instances rather longer.

We favour intravenous medication, because most of our experience is with this route of administration and we know it to be effective. The oral route has produced good results, in our series and in others, but a study of the literature suggests that it is somewhat less effective. Intramuscular administration seems ineffective.[24] The intrapleural and intraperitoneal routes have been used, with variable results.[4, 10, 10a, 24] The use of cyclophosphamide for local perfusion is mentioned by Woodhall.[35]

We are unaware of any definite time-dose relationship in the use of this drug or other alkylating agents. This concept, important in radiation therapy, may be of equal importance in the chemotherapy of cancer. At present it seems unlikely that alkylating agents, as we know them, will ever be curative; their action is non-specific, affecting all dividing cells, normal and malignant; these agents are used with the hope that normal tissue will have greater powers of recovery, to the ultimate benefit of the host. Optimum dosage remains to be determined.

For practical purposes cyclophosphamide is less toxic to the liver parenchyma than either triethylene melamine (TEM), T.S.P.A. or nitrogen mustard. Unfortunately, metastatic disease of the liver seems to be completely unaffected by this agent; the fact that drug therapy is possible should not constitute an indication for its use in hopeless cases. However, cyclophosphamide might be tried with caution in some selected cases of sensitive reticuloses with liver involvement. Only one paper to date (Bergsagel and Levin[2]) suggests that liver damage does occur and the authors of that report cite two definite examples of hepatotoxic jaundice in a series

of 118 patients, in which cyclophosphamide might be implicated.

Metastatic disease of the lung seems particularly resistant to cyclophosphamide, even when there is evidence of an effect on lesions elsewhere. Our series included 29 patients with secondary lesions in the lung, and among these, only one response was obtained with the drug alone, the case of Ewing's sarcoma.

Cyclophosphamide has a place in the management of advanced malignant disease but new lesions may appear during treatment even in cases where definite objective evidence of tumour retrogression has occurred. The persistence of certain tumour masses while others are disappearing may be related to such factors as the blood supply or the state of the tumour bed. The appearance of new lesions in other sites during maintenance therapy, or towards the end of a definitive course of treatment, is remarkable and more difficult to understand.

We have found no mention in the literature of the possibility that this drug might disturb the overall tumour-host relationship, with progression of the disease rather than improvement. This possibility deserves critical study, but we have no evidence to suggest that it has occurred.

### *Indications for Cyclophosphamide Therapy*

The indications for the use of this drug are not clear-cut at present, but we advocate its further trial in the following conditions:

#### 1. *Multiple Myeloma*

To date, no effective treatment for this disease exists. Urethane is usually tried but its value is uncertain, bearing in mind the natural history of this disease. From the literature and from our studies, cyclophosphamide is of value in about 40% of cases of myeloma. Objective improvement has been indicated by a decrease in myeloma protein and return of the serum calcium to more normal levels. One of our myeloma patients showed recalcification of bone, which was a most encouraging sign.

#### 2. *Lymphosarcoma*

Our experience with cyclophosphamide in this condition is insufficient to justify extended comment. If the response rate of 66% recorded in the literature is accepted, this agent seems to have a definite place in the management of widespread disease. In our view, radiation therapy is the treatment of choice in the early localized stage, but in those with large multiple masses a low dose of radiation therapy, combined with cyclophosphamide, should be given if practicable. Where the patient is obviously failing and anemia due to hemolysis is present, corticosteroids should be used as well.

#### 3. *Reticulum Cell Sarcoma*

Treatment of this disease is most disappointing; no therapeutically effective drug exists but sporadic good results have been reported with all of the alkylating agents. Our survey of the literature shows the remarkably high figure of 74% of patients responding to treatment with cyclophosphamide. This figure is hard to believe, and we wonder whether some cases of lymphosarcoma and other reticuloses have been included. Nevertheless, when an alkylating agent is indicated, cyclophosphamide should be tried first.

#### 4. *Hodgkin's Disease*

Subjective improvement occurs in 72% of patients with Hodgkin's disease and objective response in about 60%. Remissions seem to last longer than with nitrogen mustard, and perhaps longer than with chlorambucil. Cyclophosphamide may prove to be the drug of choice in treatment of this disease, despite the disadvantage of the alopecia that it so frequently causes. Radiation therapy is superior to drug treatment for localized disease, because its action is more certain and the duration of response longer.

#### 5. *Ovarian Cancer*

Ovarian cancer is an unpredictable disease which sometimes responds to T.S.P.A. and chlorambucil (Leukeran). The literature suggests that cyclophosphamide was effective in 48% of cases of carcinoma of the ovary where this was the only agent used; therapeutic trial is indicated in inoperable or recurrent cases. Our experience suggests that this agent may be valuable in conjunction with radiotherapy in this condition.

Since October 1960 we have had the opportunity of treating another four patients with ovarian cancer with combined cyclophosphamide and radiation therapy, and the results in three of these patients have been very encouraging.

#### 6. *Acute Leukemia*

From the literature, a response to cyclophosphamide was noted in 41 of 137 patients with acute leukemia (30%). This does not imply remission, which seems to occur in about 11 to 15% of adults and children with acute lymphatic leukemia, when they are treated with cyclophosphamide after other drugs have ceased to be effective. Weekly therapy may be more effective than daily treatment.[13] Admittedly this rate is low and the remissions have not been of long standing, but we feel it is worthwhile keeping this drug in mind for possible use in these circumstances.

#### 7. *Combination with Radiation Therapy*

The addition of cyclophosphamide to radiotherapy has already been mentioned for treatment

of patients with advanced ovarian and other cancers. We suggest that its use be investigated in selected cases of tumours which are not usually amenable to radiotherapy, particularly adenocarcinoma of the large bowel, and possibly hypernephroma. There is probably no synergistic effect betwen these therapeutic agents, but an additive effect may occur in some cases, which would give useful palliation. In a wide variety of diseases, radiotherapy and cyclophosphamide at the level of 1.4 g. weekly seems to be a safe and convenient combination. In our experience the radiation dose need not be reduced unless very large treatment fields are required.

*Contraindications*

1. Liver and lung metastases are rarely benefited; such patients should not be subjected to a prolonged course of therapy.

2. As the effect of this alkylating agent is unpredictable, it should not be used as the sole method of treatment in a disease where effective agents already exist.

3. Cyclophosphamide is slow in its action at the dosage levels used in our studies; it is not indicated in conditions such as superior vena caval obstruction or compression of the spinal cord due to tumour which require urgent treatment.

SUMMARY

The literature is reviewed and the reported responses of various forms of malignant disease to cyclophosphamide therapy are collected. Dosage schedules varied widely in the different series encountered in this review.

The toxic effects are depression of the bone marrow, nausea, and alopecia, although other toxic effects are occasionally described.

A personal series of 67 cases of advanced malignancy which have been treated is reported in detail, and the results are compared with those of other authors.

The probable indications for and contraindications to the use of this drug are discussed. In combination with radiotherapy it is safe and practicable, and merits wider use.

Supplies of cyclophosphamide (Procytox, F. W. Horner, Ltd.) were made available through the kindness of Dr. J. R. MacDougal.

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## PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

When a patient has apparently completely recovered from an acute attack of appendicitis, he may never suffer from it again, but in a certain percentage of instances the inflammation recurs. The frequency of such recurrences has been very differently gauged by different writers, and this difference of likelihood of recurrence has led to very great variation in the advice given as to the removal of the offending organ in the "quiescent period". Some authorities, such as Ochsner, believe that one decided attack is an indication for operation some three weeks after it is over, while others would wait until two or even three attacks have occurred before they would thus act. If the initial attack has been a severe one the appendix may have been destroyed by the severe inflammation, or if not, may have been so walled off by adhesions that any subsequent attack, if it should occur, would be of little danger.

Appendicectomy in the quiescent period is an operation so little attended with risk that it may be advised with little fear. No hard and fast rule can be laid down, but where an individual, who has had one well-marked attack, is apt from his occupation to be far removed from skilled surgery, it would seem wise to advise that he have his appendix removed. If, however, he lives near surgical means, then one may be justified in advising that he need not subject himself to the slight risk and several weeks of invalidism inseparable from an operation all for fear of a further attack which is as likely as not never to occur.—Robert D. Rudolf, *Canad. M. A. J.*, 1: 927, 1911.