haemoglobin S gene in the population (Allison, 1954; Raper, 1955, 1959; Garlick, 1960; Motulsky *et al.*, 1966), though there were extensive discrepancies between the number of Hb AA children who should die and the number that actually died. Subsequently evidence that there was an increased fertility among Hb AS females was proposed (Edington, 1955; Livingstone, 1957; Delbrouck, 1958; Firschein, 1961). More recently it had been suggested that a third mechanism may be operative in that there is enhanced fertility of the Hb AS male (Eaton and Mucha, 1971).

The data of Edington (1955) from Ghana and of Firschein (1961) from British Honduras showed that mothers with the sickle-cell trait had a fertility ratio which could account for the value required to maintain the local sickle-cell trait frequency. Edington also showed that the stillbirth rate for a hospital population of mothers with Hb AS was slightly lower, but the figures were not at acceptable levels of statistical significance. In the current study the finding of a low frequency of Hb AS mothers who had an antepartum death of their fetus showing no significant pathological lesion supports the observations of other workers that the incidence of abortion and antepartum stillbirths is lower among such mothers (Garnham, 1949; Bruce-Chwatt, 1952).

With the generally accepted evidence that there is a higher fertility rate among mothers with the sickle-cell trait, and in the absence of data other than that from "selected" hospital populations, it is justified, at present, to assume that greater perinatal loss associated with the maternal sickle-cell trait is an observation of relevance to the practical management of the labour of an individual possessing the trait but that the overall perinatal loss does not influence the balanced polymorphism of the haemoglobin S gene.

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PRELIMINARY COMMUNICATIONS

Multiple Drug Therapy for Disseminated Malignant Tumours

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Summary

Forty patients with various disseminated malignant tumours were treated with up to six antitumour drugs given for periods not exceeding 24 hours. Complete or partial objective tumour regression was achieved in 20 patients. No regression occurred in the remaining 20. Treatment given in this way

seemed to be at least as effective as other multiple drug regimens and had the following advantages: (1) toxicity was reduced to a minimum and no access was needed to sterile rooms or platelet transfusions since severe bone marrow depression did not occur, and (2) the patients spent only a very short time in hospital.

Introduction

In recent years it has become apparent that antitumour drugs are often more effective when given in combination than when given singly or in sequence. This has been observed particularly in acute leukaemias and malignant lymphoma. Thus the treatment of these diseases with single agents produces complete remission in from 25 to 50% of patients, whereas with judicious combinations of three or four drugs the proportion of complete remissions has been increased to 85% in acute lymphoblastic leukaemia and Hodgkin's disease. These observations have naturally led clinicians to apply combination schedules to patients with disseminated solid tumours which could not be treated by local methods such as surgery or radiotherapy. Thus, for example, Costanzi and Coltman (1969)

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reported regressions in some patients given four drugs over five days, and similar regimens are currently being used at various centres. Such regimens, however, are usually given over several days and are often quite toxic to the patient's normal tissues.

Bruce *et al.* (1966) showed that under certain experimental conditions considerable advantages resulted if antitumour drugs were given over short periods of time. Not only was a greater selectivity achieved against tumour cells but also far less toxicity occurred to normal bone marrow. These advantages were attributed to kinetic differences between a certain proliferating fraction of the tumour cells compared with the corresponding fraction of normal bone marrow cells. If these experimental findings are at all relevant to the treatment of human tumours, then giving drugs over a short period of time might be expected to show similar advantages. Some potential clinical applications of this approach have been summarized by Bergsagel (1969), who has also shown that vincristine, cyclophosphamide, and methotrexate can be given optimally in this way (personal communication). In addition, we have already shown that up to 20,000 (twenty thousand) mg of methotrexate can be given to patients over 24 hours without toxicity (Goldie *et al.*, 1971). A dose of this kind, of course, is far greater than that customarily given, and certain specific precautions have to be taken in order to prevent side effects.

The treatment schedule described in this paper was designed according to Bruce's experimental principle, and this study might therefore be expected to answer the following questions: (1) Can the toxicity of multiple drug schedules be reduced by giving the drugs over 24 hours? and (2) Is the therapeutic effect of the drugs lessened if they are given in this way? In addition, we wished to see if any particular kind of tumour responded especially well to this regimen.

Patients and Methods

Forty patients have been treated so far—22 at the Royal Marsden Hospital, London, and 18 at St. Michael's Hospital, Toronto. Nearly all were in poor general condition. All conformed to the following criteria:

- (1) The diagnosis must have been established beyond all doubt by a competent histopathologist.
- (2) All usual methods of treatment—that is, surgery, radiotherapy, or chemotherapy—as customarily given must either have been tried or else have been considered impracticable because of the extent of the disease.
- (3) All assessments of response were objective, and were based on x-ray changes or direct measurement of the tumour where possible. In patients with testicular tumour, all of whom had pulmonary secondaries, urinary excretion of chorionic gonadotrophin was used as an additional guide to progress. When liver secondaries were present liver scans were also done, but were not themselves considered as evidence of objective improvement.
- (4) Bone marrow and creatinine clearance tests were carried out before treatment was given. If marrow function was severely impaired owing to previous drug or irradiation therapy treatment was postponed until the marrow had recovered. If there was any doubt at all about marrow function the doses of cyclophosphamide and fluorouracil were halved for the first treatment and this applied to all patients who had had thoracic, abdominal, or pelvic radiotherapy.

There is no generally accepted definition of response in patients with disseminated malignant disease. Obviously a partial regression lasting a year is better for the patient than a complete regression lasting for a month. Partial responses of this kind are difficult to qualify, whereas complete regression is a reasonable index of biological response. In this paper complete regression, or remission, means complete disappearance of all objective evidence of disease with restoration of the patient to normal function. Partial regression means a reduction of at least 25% in some measurable aspect of the disease with some improvement in function but falling short of com-

plete regression. Because all these patients had extensive disease, reductions of 25% were always obvious. This, of course, would not have been the case if only small nodules were being measured. No regression means no objective evidence of improvement in any measurable aspect of the disease. Subjective improvements of pain or other symptoms, however definite, were counted as non-regressions.

The reasons for choosing the particular drugs in the regimen described were that each drug has a different biochemical locus of action in the cell growth cycle and also that they represent each of the two main types of antitumour agent described by Bruce *et al.* (1966).

Administration

Though the drugs were given according to the kinetic principles indicated above, two separate schedules were used.

SCHEDULE 1

Patients in this group were given the following six drugs in the doses indicated: cyclophosphamide 600 mg/m² to a maximum of 1 g, fluorouracil 500 mg/m² to a maximum of 750 mg, actinomycin D 0.25 mg/m² to a maximum of 0.5 mg, vincristine 1 mg/m² to a maximum of 2 mg, methotrexate 400 mg to all patients, and cytosine arabinoside 400 mg to all patients. These drugs were given as follows:

One hour before treatment began the patient was given 400 mg of chlorpromazine orally, and a normal saline drip was set up. On the same drip stand a second litre of normal saline was set up with its own giving set separately and left for use as a side drip when necessary. At the beginning of the treatment (0 hours) the cyclophosphamide, fluorouracil, actinomycin D, and vincristine were injected sequentially into the rubber tubing of the main drip, each injection being given as a single push. A small amount of normal saline was run through between each injection to prevent mixing of the drugs inside the rubber tubing. Immediately after these injections the saline drip was changed to a 1-litre bottle of normal saline containing 200 mg of methotrexate. This litre ran for 12 hours and was immediately followed by another litre of N saline also containing 200 mg of methotrexate, which ran for a further 12 hours, so that altogether 400 mg of methotrexate was given in 2 litres of N saline over 24 hours.

Three hours from the beginning of treatment—that is, four hours after the first dose—another 400 mg of chlorpromazine was given orally. Further injections of chlorpromazine 100 mg were then given intramuscularly at four-hourly intervals as necessary to control vomiting. At 0, 6, 12, and 18 hours, cytosine arabinoside 100 mg was injected through the side drip so that each injection of cytosine could be separated from the main stream of methotrexate by a small bolus of saline run through before and after the cytosine injection. At 24 hours—that is, when the second bottle of methotrexate drip was discontinued 120 mg of folic acid (calcium Leucovorin) was given intravenously through the side drip. The drip was then taken down. The patient was then given 15 mg of folic acid intramuscularly for five doses at six-hourly intervals.

Patients whose creatinine clearance was less than 80 ml/min or whose bone marrow was marginally hypoplastic were given 200 mg of folic acid intravenously in addition to having their doses of cyclophosphamide and fluorouracil halved. All patients were allowed home after the fifth intramuscular injection of folic acid. Peripheral blood counts were done 12 days from the day on which the treatment ended. The next course of treatment was given exactly 28 days from the beginning of the first treatment and every 28 days subsequently provided that an immediate pretreatment peripheral blood count had returned to pretreatment levels. If any evidence of peripheral neuropathy was present (such as diminished tendon reflexes) vinblastine 5 mg was given instead of vincristine.

SCHEDULE 2

This was similar to schedule 1 except that (a) only one-half the dose of methotrexate was given—that is, 100 mg/m²—to

a maximum of 200 mg over 24 hours; (b) actinomycin D was given only to those patients with tumours of mesodermal origin—it was then given in a dose of 0.6 mg/m² to a maximum of 1 mg; (c) cytosine arabinoside was not used at all; (d) prochlorperazine was used to control vomiting instead of chlorpromazine; and (e) fluorouracil was given to a maximum of 1 g.

Results

The results were very similar for both schedules and are shown in Tables I-III. Evidence of improvement often did not occur until six weeks had elapsed—that is, until two weeks after the second treatment—though this was not always the case.

TABLE I—Complete Regressions (Remissions)

Diagnosis	Sex	Age	Remission Time (Months)
<i>Schedule 1</i>			
Carcinomatous peritonei + ascites ..	M.	11	6*
Fibrosarcoma mandible ..	F.	22	10*
Embryonal cell carcinoma ..	F.	22	2
Ca breast ..	F.	31	6*
Ca bladder ..	M.	62	3
<i>Schedule 2</i>			
Ca lung ..	M.	64	6
Ca lung ..	M.	67	2*
Ca breast ..	F.	68	8*
Ca breast ..	F.	43	4*
Rhabdomyosarcoma ..	F.	20	5
Hypernephroma ..	F.	22	1

* Patient is still in remission.

The first case under schedule 1 had cells which were too primitive to classify or to indicate the tissue of origin. Of the breast carcinoma patients, one had pulmonary and bony secondaries, one had pulmonary secondaries only, and one had extensive local recurrence. The patient with hypernephroma died from a pulmonary embolism while in complete remission.

TABLE II—Partial Regressions

Diagnosis	Sex	Age	Remission Time (Months)
<i>Schedule 1</i>			
Ca ovary with ascites ..	F.	55	9
Ca bladder ..	M.	70	7*
Teratoma testis ..	M.	22	2
Teratoma testis ..	M.	21	1
Ca breast ..	F.	60	8
Plasmacytoma ..	M.	55	2*
<i>Schedule 2</i>			
Ca breast ..	F.	48	5
Ca lung ..	M.	60	10*
Uterine sarcoma ..	F.	64	2

* Disease is controlled.

In all cases except the second and fifth listed under schedule 1 the reduction in size was considerably greater than 25%.

TABLE III—Diagnosis and Number of Patients in Each Schedule Who Failed to Respond to Treatment

Schedule 1	Schedule 2
Ca G.I. tract .. 3	Ca G.I. tract .. 4
Ca lung .. 1	Ca lung .. 1
Ca bladder .. 2	Ca breast .. 1
Leiomyosarcoma .. 1	Melanoma .. 1
Ca ovary .. 1	Ca ovary .. 1
Ca prostate .. 1	Lymphangiosarcoma .. 1
Giant cell tumour soft parts (W.H.O. classification) 1	
Squamous Ca head and neck 1	

SIDE EFFECTS

Though one-half of the patients slept throughout, the other half vomited, mainly during the first eight hours of the treatment. No patient vomited more than six times. All patients had

alopecia, but in those who survived more than six months the hair always grew again. Wigs were provided as required. Depression of tendon reflexes attributed to vincristine occurred in one patient. The day following treatment the patients were drowsy, presumably from the large doses of antiemetics. Sixteen of them were slightly anorexic for seven days after the treatment, though they were able to eat. Two patients had transient diarrhoea during the treatment which stopped after 36 hours and was subsequently prevented with codeine phosphate 120 mg orally before the next treatment. For the remaining three weeks before the next treatment no symptoms attributable to the drugs occurred in any patients.

Maximal depression of the total white cell count and platelets virtually always occurred on the twelfth day from the end of treatment (see Chart). Thereafter both platelets and white count began to rise and were nearly always normal by 21 days.

Composite peripheral blood chart of five treatment cycles from five different patients.

By 28 days both counts were back to pretreatment levels in all patients. This cycle was repeated regularly in any given patient so that peripheral blood count 12 days after the first treatment is usually the only precaution required. In some patients the haemoglobin level tended to fall slowly over several months, and these cases were given blood transfusions immediately after one of their monthly treatments as required. In no patient did severe bone marrow depression occur.

Discussion

These results confirm the experimental and clinical findings of Bruce *et al.* (1966) and Bergsagel (1969) by showing that the toxicity of antitumour drugs can be reduced to a minimum provided that (a) the drugs are given over a short period of time, (b) the next course of treatment is not given until the bone marrow function returns to its pretreatment level as shown by peripheral blood charts, and (c) the precautions

indicated are rigorously observed. In this series this lack of toxicity had several obvious advantages. Because severe bone marrow depression did not occur no access was needed to reverse barrier rooms or to platelet transfusions. In addition, most patients spent only a short time in hospital—that is, three or four days out of 28. Furthermore, though side effects did occur, the quality of the patient's life was not impaired to the extent seen with certain other multiple drug regimens. This meant that even if the treatment should fail, therapy could still be offered to patients in the knowledge that at least it would not make them any worse than they were already. Since the treatment has proved safe over 160 treatment cycles in 40 patients we feel that it should now be used much earlier than has been the case in this preliminary study, perhaps as soon as evidence of metastases first appears.

The overall regression rate in this series seems to be at least comparable to that achieved by other more toxic regimens. There is therefore no evidence that the antitumour effect of these drugs is lessened by giving them in this way. The similarity in response rate between schedules 1 and 2 suggests that the addition of cytosine arabinoside may not contribute any significant antitumour effect.

Thus in answer to the questions posed in the introduction we conclude that the toxicity of multiple antitumour drug

schedules can be reduced to acceptable levels without lessening their antitumour effect. As to whether there exists a particular kind of tumour which might respond especially well to such treatment, we have the impression that carcinomas of the breast and bladder may do relatively well. However, we propose to extend the study to include a further 60 patients to see if such a subgroup can be definitely identified.

L.A.P. wishes to thank all consultants at the Royal Marsden Hospital who referred patients for this trial, particularly Dr. D. A. G. Galton and Dr. E. Wiltshaw, and also wishes to acknowledge the excellent standard of nursing care on Wolrige Ward, Royal Marsden Hospital, London.

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Requests for reprints should be addressed to Dr. L. A. Price.

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MEDICAL MEMORANDA

Myasthenia with Systemic Lupus and Palmoplantar Keratosis

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A case is described here in which a patient with myasthenia gravis developed tylosis and features of systemic lupus erythematosus.

Case Report

A 20-year-old mill labourer presented in 1963 with a six-month history of increasing weakness of the legs. His previous health had been excellent and the family history contained nothing abnormal. He was noted to have some facial wasting and slight, non-tender enlargement of cervical and axillary lymph nodes. The muscles were normal in appearance but fatigued quickly. Normal power was restored by an injection of edrophonium. The E.S.R. was 15 mm/hr (Westergren) and the W.B.C. 3,700/mm³. Treatment with neostigmine 15 mg four times daily was started.

The weakness slowly returned and ascended, leading him to present again in July 1970 with difficulty in speaking, swallowing, and closing his eyes. In the preceding three years there had been intermittent painful swelling of the knees. Sometime during this period he had noticed painless thickening of the palmar and plantar skin. The increasing weakness had forced him to take lighter employment as a telephonist.

The skin of the palms and soles was transformed into a uniformly thickened orange-yellow keratinized layer. The skin else-

where and the hair and nails were normal. His appearance suggested facial muscle wasting and there was wasting of the lumbar paraspinal muscles. The muscles generally felt flabby and hypotonic, and they were weak and fatigued very quickly. Non-tender enlargement of the cervical, axillary, and inguinal nodes was palpable and a small effusion was present in the right knee.

Edrophonium 10 mg intravenously produced a dramatic response, restoring the muscular strength to normal for one minute. The E.S.R. was 63 mm/hr and the W.B.C. 4,000/mm³. A high titre of antinuclear factor was present and an L.E. cell preparation was strongly positive. Serum IgG 2,012 mg/100 ml, IgM 340 mg/100 ml. Muscle biopsy showed lymphorrhages characteristic of myasthenia gravis and electromyography demonstrated typical motor response fatigability.

The anticholinesterase therapy was increased to neostigmine 15 mg six times daily plus pyridostigmine 60 mg three times daily. Azathioprine 100 mg daily was started. Improvement in muscle power was obtained and though this was not of normal strength he was able to continue work. The serum abnormalities persisted—E.S.R. 44 mm/hr, antinuclear factor + + +, IgG 1,688 mg/100 ml, IgM 424 mg/100 ml.

His parents, four brothers, and two sisters were examined and found to be healthy. None had tylosis, myasthenia, or systemic lupus erythematosus or were positive for antinuclear factor.

Comment

Hyperkeratosis of the palms and soles occurs in pityriasis rubra pilaris, but the skin elsewhere, particularly of the backs of the hands, usually shows the characteristic follicular keratosis. In this patient the skin other than that of the palms and soles was normal. The keratosis resembled that seen in the familial tyloses. These familial lesions may be seen in association with other ectodermal dysplasias (as in the Unna-Thost, Papillon-Lefèvre, and Meleda diseases), with tumours of viscera of foregut origin (oesophagus (Howel-Evans *et al.*, 1958), bronchus (Parnell and Johnson, 1969), larynx and stomach (Haines, 1967), or with hypertrophic spondylitis (Beardwell, 1969).

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