SEVENTY-FIVE CASES OF SOLID TUMOURS TREATED BY A MODIFIED QUADRUPLE CHEMOTHERAPY REGIME

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SUMMARY.—Seventy-five cases of malignant solid tumours treated by a quadruple chemotherapy regime are described. These tumours originated in the breast, head and neck, bronchus, genital tract, cutaneous melanoma, soft tissue and gastro-intestinal tract. All 14 patients with breast carcinoma underwent remission and in 6 this was complete. Significant remissions were seen in gastro-intestinal and head and neck malignancies, and also in the soft tissue group. A short response was noted in 6 of 14 cases of bronchial carcinoma. Malignant melanoma, testicular, ovarian and cervical carcinomata failed to respond.

In all, 40 of 75 patients underwent objective remission.

Results of treatment of solid tumours (as distinct from reticuloses and leukemias) by individual chemotherapeutic agents have been disappointing, although short remissions in 50% of breast cancer cases have been observed with cyclophosphamide (Kunkler et al., 1968) and 30% with 5-fluorouracil (Heidelberger and Ansfield, 1963). It was at one time hoped that concentration of dose by intra-arterial techniques would improve the response rate for localised tumours, but this method has fallen into disfavour at this Centre owing to frequent relapses and a disturbing incidence of complications. The position of intra-arterial chemotherapy, certainly in head and neck cancer, has further been weakened by the results of intermittent high dose intravenous injections of Methotrexate, which have given a 57% remission rate in one series (Leone et al., 1968).

In an effort to improve the generally disappointing results associated with single cytotoxic agents, intravenous injection of a combination of the 4 cytotoxic agents, cyclophosphamide, Methotrexate, Vincristine and 5-fluorouracil, originally advocated by Constanzi and Coltman (1969) has been selected, though in a reduced dosage (Table 1).

EXPLANATION OF PLATES

Fig. 1.—Nodular carcinoma en cuirasse before (A and B) and 3 months after (C and D) chemotherapy.

Fig. 2.—Breast carcinoma. Widespread diffuse opacities both lung fields, before (A) and 2 months after (B) chemotherapy.

Fig. 3.—Carcinoma of bronchus with cutaneous metastases before (A) and 1 month after (B) chemotherapy, showing partial response.

Fig. 4.—Cutaneous deposits from alveolar rhabdomyosarcoma before (A) and 2 months after (B) chemotherapy. Mediastinal deposits before (C) and 2 months after (D) chemotherapy.
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Table I.—Quadruple Chemotherapy

| Drug                        | Modification of dosage in the adult suggested by the authors |
|-----------------------------|---------------------------------------------------------------|
| 300 mg.—2 doses days 1 and 5| Cyclophosphamide . 2–300 mg.—2 doses days 1 and 5           |
| 0.5 mg./kg./day—2 doses days| Methotrexate . 0·25 mg./kg./day—2 doses days 1 and 4         |
| 0·025 mg./kg./day—2 doses days| Vincristine . 0·015 mg./kg./day—2 doses days 2 and 5         |
| 10 mg./kg./day, daily       | 5-Fluorouracil . 7·5 mg./kg./day, daily for 5 days           |

Constanzi and Coltman (1969) suggested that the interval between the first and second course should be 2 weeks, and thereafter 4 weeks. This regime was followed in the early cases, but we now find that a 4-weekly interval throughout is effective. The modified schedule was adopted because severe toxicity was seen in early cases treated according to the original protocol. Further reduction has been made in individual cases for any of the following reasons:

1. Old age.
2. Previous chemotherapy or radiotherapy.
3. Widespread bone marrow involvement.
4. General ill health.

In the series of Constanzi and Coltman (1969) treatment was continued for an overall maximum period of 6 months. In the present series patients have been under treatment for periods up to 18 months.

Clinical material

Seventy-five patients with solid tumours have been treated: Table II indicates

Table II.—Types of Tumour Treated and Degree of Response Achieved

| Tumour Type              | Complete | Partial | Failure | Total |
|--------------------------|----------|---------|---------|-------|
| Breast carcinoma         | 6        | 8       | 0       | 14    |
| Head and neck carcinoma  | 1        | 7       | 2       | 10    |
| Bronchial carcinoma      | 0        | 8       | 6       | 14    |
| Ovarian carcinoma        | 0        | 0       | 4       | 4     |
| Testicular carcinoma     | 0        | 0       | 4       | 4     |
| Cervical carcinoma       | 0        | 0       | 3       | 3     |
| Malignant melanoma       | 0        | 0       | 10      | 10    |
| Soft tissue sarcoma      | 0        | 5       | 1       | 6     |
| Various                  | 0        | 1       | 1       | 2     |
| Nephroblastoma           | 0        | 0       | 1       | 1     |
| Hepatoma                 | 0        | 0       | 1       | 1     |
| Stomach carcinoma        | 1        | 1       | 0       | 2     |
| Large bowel carcinoma    | 1        | 1       | 1       | 3     |
| Bone carcinoma           | 0        | 0       | 2       | 2     |
| Total                    | 9        | 34      | 32      | 75    |

the type of tumour and the degree of response achieved. Objective response was graded as:

1. Complete
2. Partial
3. Failure
The Karnofsky scale, Table III (Karnofsky and Burchenal, 1948) to indicate subjective response and improvement in the general condition of the patient.

**Table III.—Karnofsky's Rating for Chemotherapy Response**

| Rating                                        | %  |
|-----------------------------------------------|----|
| Normal                                        | 100|
| Minor signs or symptoms                       | 90 |
| Normal activity with effort                   | 80 |
| Unable to carry on normal activity, but cares for self | 70 |
| Requires occasional assistance with personal needs | 60 |
| Requires considerable assistance and medical care | 50 |
| Disabled                                      | 40 |
| Severely disabled and hospitalized            | 30 |
| Very sick: active supportive treatment necessary | 20 |
| Moribund                                      | 10 |
| Death                                         | 0  |

**Complications**

Thirty-six cases were treated without side effects. In the remainder the most frequent was evidence of toxicity, leucopenia (2000 white cells or less), followed by alopecia, nausea and vomiting, stomatitis and peripheral neuropathy.

Bone marrow depression (16 cases) was no more frequent or profound than with standard courses of, *e.g.* Methotrexate, 5-fluorouracil or cyclophosphamide used singly.

Alopecia occurred in 15 cases, mostly in the early part of the series. It is possible that this incidence would have been greater had it not been for a scalp tourniquet applied during and for 5 minutes after injection.

In 3 patients with peripheral neuropathy Vinblastine was substituted for Vincristine in view of the known neurotoxic effect of the latter compound.

Three patients failed to complete their treatment because of side effects.

**RESULTS**

**Breast Carcinoma (Table IV)**

These were patients with advanced and uncontrolled disease, which had previously been treated by hormones or adrenalectomy, and/or 5-fluorouracil or cyclophosphamide by injection. All cases showed some response; in 6 out of 14 this was complete and maintained for more than 6 months.

Subjective improvement was manifested by relief of bone pain and improvement in general well-being. Objective remission was observed in chest wall recurrence (Fig. 1A, B, C, D), in liver deposits and in pulmonary metastases.

In 1 patient lung function studies were carried out before and after 2 courses of chemotherapy. They showed an increase in total lung and initial residual capacity and in maximum expiratory flow rate (Table V, Fig. 2A, B). Chest X-ray confirmed some clearing of disease.

Two patients were considered too ill for endocrine ablative procedure, but following good objective and subjective response to quadruple chemotherapy, successfully underwent bilateral adrenalectomy and oophorectomy. Remission continued without further chemotherapy in both cases.

Four patients with carcinoma en cuirasse were treated; 1 showed complete response and 3 partial response. In our experience this type of disease has proved unresponsive to single agent chemotherapy.
Head and neck carcinoma (Table VI)

The palliation of uncontrolled head and neck cancer presents a challenging problem to the chemotherapist. Intra-arterial methods have fallen from favour in this Centre, and, as already mentioned, single intravenous weekly injections of Methotrexate have produced comparable results with far less morbidity. One of us (I.H.) has observed objective response in 50% of patients treated by intravenous Methotrexate, but palliation was generally short-lived, seldom exceeding 3 months.

Quadruple chemotherapy has been used mainly in those cases showing failure of control with, or relapse following intravenous Methotrexate. Further remission has been achieved in 6 of 10 patients, lasting up to 6 months in 1 case.

In view of these findings we suggest that quadruple chemotherapy should replace the use of a single agent in this group of cases.

Bronchial carcinoma (Table VII)

Fourteen cases have been treated. None showed complete regression of disease, but in 8 patients there was a partial, short-lived, response (maximum duration 3 months). Rapid, though transient, regression of cutaneous metastases was noted in 3 patients (Fig. 3A, B). One patient with superior vena cava obstruction, which had relapsed after radiotherapy, was treated (by injection into the veins of the uninvolved lower limbs) with rapid resolution of symptoms.

Our experience suggests that the results may not be better than those following single weekly intravenous injections of cyclophosphamide, though admittedly this series is small.

Genital carcinoma (Table VIII)

Four testicular and 4 ovarian carcinomas were treated, without effect. Wiltshaw (1965) claimed 43% remission for at least 2 months in ovarian cancer using chlorambucil; Bateman (1962) reported a similar remission rate with ThioTepa, and Burns et al. (1969) claimed 50% response in carcinoma of the ovary treated with phenylalanine mustard. The poor response to quadruple chemotherapy is therefore surprising.
### Table IV.—Fourteen Cases of Breast Carcinoma

| Patient | Age | Sex | Site of metastases | Previous chemotherapy and/or hormone therapy | Number of courses | Side effects | Karnofsky Objective | Duration of response (months) | Comment |
|---------|-----|-----|---------------------|---------------------------------------------|------------------|-------------|---------------------|-------------------------------|---------|
| L.D.    | 63  | F   | Carcinoma-lymphangitis, soft tissue bone | Norsthisterone 5-fluorouracil | 5 | Alopecia | Complete | 80 | 90 | 6 | Alive, successful adrenalectomy and oophorectomy 5 months after quadruple |
| M.D.    | 43  | F   | Bone | 5-fluorouracil adrenalectomy | 8 | Alopecia | Partial | 80 | 90 | 8 | Alive |
| D.B.    | 54  | F   | Soft tissue en cuirasse | Control with Nandrolone a year 5-fluorouracil cyclophosphamide | 9 | Alopecia | Partial | 80 | 90 | 9 | Alive |
| B.G.    | 56  | F   | Soft tissue en cuirasse | 5-fluorouracil methotrexate cyclophosphamide | 12 | Temporary alopecia | Complete | 90 | 100 | 12 | Alive |
| B.W.    | 47  | F   | Bone | Nandrolone 5-fluorouracil cyclophosphamide | 9 | Alopecia anaemia leucopenia | Partial | 70 | 90 | 9 | Alive, relief of pain |
| Name  | Age | Sex | Diagnosis and Treatment | Therapy | Response | Complete | Partial | Alive/Mortality |
|-------|-----|-----|--------------------------|---------|----------|----------|---------|----------------|
| H.C.  | 45  | F   | Soft tissue, hepatic enlargement | Norethisterone 5-fluorouracil | 3 | Vomiting | Partial | 80/90 | Alive, successful adrenalectomy and oophorectomy after 3rd course |
| P.P.  | 54  | F   | Soft tissue en cuirasse hepatic enlargement | Bilateral oophorectomy and adrenalectomy 2 months before quadruple | 7 | Nausea | Complete | 70/100 | Alive |
| M.R.  | 54  | F   | Soft tissue en cuirasse | Prednisone 5-fluorouracil methotrexate ICRF 169 | 9 | Alopecia, mental depression | Partial | 80/90 | Alive |
| E.B.  | 56  | F   | Soft tissue, pulmonary metastases en cuirasse | Norethisterone | 6 | Leucopenia | Partial | 50/80 | Alive, relief of dyspnoea |
| H.E.  | 60  | F   | Soft tissue bone | Nandrolone | 4 | Nil | Partial | 60/90 | Alive, relief of pain |
| D.B.  | 65  | F   | Hypercalcaemia, bone en cuirasse | Nandrolone | 4 | Nil | Partial | 90/90 | Alive, relief of pain, Normal calcium |
| M.McC. | 75  | F   | Soft tissue en cuirasse cyclophosphamide | Nandrolone | 4 | Nil | Partial | 90/90 | Alive |
| V.E.  | 74  | F   | Soft tissue cyclophosphamide | Nandrolone | 6 | Nephritis, mental depression, leucopenia | Complete | 80/90 | Alive |
| L.O.  | 70  | F   | Bone, brain Nandrolone, bilateral adrenalectomy | Nandrolone, bilateral adrenalectomy | 6 | Peripheral neuropathy | Complete | 80/90 | Alive, relief of pain |
### Table VI.—Ten Cases of Head and Neck Carcinoma

| Patient | Age | Sex | Diagnosis | Previous treatment | Number of courses | Side effects | Objective | Karnofsky | Duration of response (months) | Comment |
|---------|-----|-----|-----------|--------------------|------------------|--------------|-----------|----------|-----------------------------|---------|
| J.C.    | 64  | M   | Carcinoma of larynx | Local recurrence after radiotherapy and local surgery | 6                | Nil          | Partial   | 60       | 80                          |         |
| E.W.    | 64  | M   | Carcinoma of larynx | Local recurrence after radiotherapy and local surgery | 4                | Nil          | Partial   | 50       | 50                          | 3       | Died 9 months after starting quadruple. Chemotherapy at 5 months, changed to Bleomycin |
| J.S.    | 36  | M   | Carcinoma of pyriform fossa | Local recurrence after radiotherapy | 1                | Nil          | Failure   | 30       |        | 3 | Died during 1st course |
| J.R.    | 69  | M   | Carcinoma of floor of mouth | Local recurrence after radical radiotherapy. Failure of control with i.v. Methotrexate | 3                | Nil          | Partial   | 70       | 70                          | 3       | Patient refused to continue with the regime |
| E.E.    | 69  | F   | Carcinoma of lip     | Recurrence after radiotherapy, local recurrence after plastic surgery. Failure of control with i.v. Methotrexate | 3                | Nil          | Partial   | 60       | 70                          | 3       | Died of bronchial pneumonia |
| Name  | Age | Sex | Diagnosis                                                                 | Treatment                                                                 | Response | Complete | Duration | Comments                                     |
|-------|-----|-----|---------------------------------------------------------------------------|--------------------------------------------------------------------------|----------|----------|----------|----------------------------------------------|
| J.B.  | 64  | M   | Carcinoma of oral cavity with cervical gland metastases                  | Recurrence in block dissection of neck, failure of control with i.v. Methotrexate | 5        | Nil      | 90       | 100, 6, Continues in remission with non-active disease |
| G.B.  | 58  | M   | Carcinoma of nasopharynx with cervical gland metastases                  | Radical radiotherapy, oral Methotrexate and ICRF 159 No control, i.v. Methotrexate control 3 months | 3        | Nil      | 50       | 60, 3, Died 4 months after starting quadruple |
| H.H.  | 65  | F   | Carcinoma of floor of mouth                                             | Radical radiotherapy. Control with i.v. Methotrexate for months           | 2        | Leucopenia| Partial  | 50, 50, Nil, Died 3 months after starting quadruple |
| G.M.  | 30  | M   | Recurrence of basal cell carcinoma of the face, with pulmonary metastases | Plastic surgery                                                          | 2        | Nil      | Failure  | 60, 60, Nil, Died 1 month after starting quadruple |
| F.R.  | 52  | F   | Leukoplakia, carcinoma of cervical node metastases                       | Radium implant. External radio-nodes, i.v. Methotrexate                  | 3        | Leucopenia| Partial  | 50, 50, 2, Died 3 months after starting quadruple |
Three cases of cancer of the cervix were also treated and failed to respond.

*Malignant melanoma* (Table IX)

Ten cases of malignant melanoma were treated without response, failing to substantiate the encouraging results suggested by Constanzi and Coltman (1969). Seven patients survived for more than 6 months, but it is unlikely that quadruple chemotherapy altered the natural history of their disease. It could be argued that our modification of the dose regime contributed to these poor results, but our overall clinical impression is that this drug combination is of little value in malignant melanoma.

*Soft tissue sarcoma* (Table X)

The value of chemotherapy in soft tissue sarcoma is not generally recognised, although Wiltshaw (1967) has reported benefit following oral Methotrexate. Arterial infusion or perfusion may also produce regression in these lesions (Newton, 1967).

We have treated 6 patients, using the quadruple regime. A boy, aged 14, with metastases from an alveolar rhabdomyosarcoma involving mediastinum, liver, pancreas and skin, showed complete clinical regression within 2 months of starting treatment. This patient continued in reasonably good general health for a further 15 months, but isolated recurrences in the right inguinal region, pancreas (proven at laparotomy) and mediastinum required local radiotherapy (Fig. 4). Unfortunately this patient has now died from intestinal haemorrhage, 20 months after starting chemotherapy.

Four other cases continued to show partial response.

One case only, a leiomyosarcoma, failed to show objective response.

*Carcinoma of gastrointestinal tract* (Table XI)

Two patients with carcinoma of the stomach and 2 with carcinoma of the colon, and 1 with squamous carcinoma of the ano-rectal junction have been treated. All showed some response; this was clinically complete in 1 case of carcinoma of the stomach who remained in remission for 3 months, eating normally and gaining weight. Barium meal examination showed reduction in size of the growth.

The patient with metastatic carcinoma of the ano-rectal junction is now in complete remission, 6 months after commencement of treatment.

*Miscellaneous* (Table XII)

No benefit followed treatment in the remainder of the series, which included patients with nephroblastoma, hepatoma and bone sarcoma.

**DISCUSSION**

Seventy-five patients have been treated by a modification of a regime originally reported by Constanzi and Coltman (1969). This modification was necessary because of unacceptable toxicity in our earlier cases. Using the modified regime, treatment now present no undue problems of toxicity, yet still retains a therapeutic effect. It is practical to treat the majority of cases as out-patients. The most troublesome side effect (especially for female patients) is alopecia, 20%.
### Table VII.—Fourteen Cases of Bronchial Carcinoma

| Patient | Age | Sex | Site of metastases | Number of courses | Side effects | Karnofsky Objective | Karnofsky Pre- Post- | Duration of response (months) | Comment |
|---------|-----|-----|---------------------|-------------------|--------------|---------------------|-------------------|-------------------------------|---------|
| H.D.    | 62  | M   | Cutaneous           | 4                 | Leucopenia   | Partial            | 70                | 80                           | 3       | Died after 4th course         |
| E.H.    | 55  | M   | Superior venacaval obstruction | 4 | Nil | Partial            | 60                | 80                           | 3       | Died after 4th course         |
| R.McB.  | 64  | M   | Cerebral            | 2                 | Nil          | Failure            | 50                | 50                           | Nil     | Died after 2nd course         |
| M.McL.  | 64  | F   | Cutaneous           | 5                 | Nil          | Partial            | 80                | 80                           | 3       | Died after 5th course         |
| F.M.    | 55  | M   | Cerebral            | 2                 | Nil          | Failure            | 50                | 50                           | Nil     | Died after 2nd course         |
| K.      | 52  | M   | Lymph nodes         | 3                 | Nausea       | Failure            | 70                | 70                           | Nil     | Died 3 months after 3rd course. Treatment abandoned |
| W.H.    | 43  | M   | Visceral            | 2                 | Nil          | Partial            | 80                | 80                           | 2       | Died 1 month after 2nd course |
| M.A.    | 34  | F   | Lymph nodes         | 2                 | Nil          | Failure            | 30                | 20                           | Nil     | Died after 2nd course         |
| W.M.    | 64  | M   | Bone                | 2                 | Nil          | Failure            | 60                | 60                           | Nil     | Died after 2nd course         |
| H.C.P.  | 60  | M   | Bone                | 2                 | Alopecia     | Partial            | 50                | 60                           | 1       | Died after 2nd course         |
| W.T.H.  | 65  | M   | Cutaneous           | 1                 | Nil          | Failure            | 60                | 50                           | Nil     | Died after 1st course         |
| N.B.    | 47  | M   | Cutaneous           | 2                 | Stomatitis   | Partial            | 60                | 80                           | 1       | Continues in remission        |
| J.E.    | 45  | F   | Cutaneous,          | 2                 | Nil          | Partial            | 60                | 70                           | 1       | Died after 2nd course         |
|         |     |     | superior venacaval obstruction |               |             |                    |                   |                               |         |
| G.B.    | 45  | M   | Bone                | 4                 | Leucopenia   | Partial            | 50                | 50                           | 3       | Died after 4th course         |
TABLE VIII.—Eleven Cases of Genital Carcinoma

| Patient | Age | Sex | Previous treatment | Number of courses | Side effects | Karnofsky Objective | Duration of response | Comment |
|---------|-----|-----|-------------------|------------------|--------------|---------------------|---------------------|---------|
|         |     |     |                   |                  |              | Pre- % | Post- % |                     |         |
|         |     |     |                   |                  |              |                     |                     |         |
| Ovarian carcinoma | | | | | | | | |
| F.S. | 66 | F | Radiotherapy alkylating agents | 1 | Nausea | Failure | 30 | 0 | Nil | Died 2 weeks after starting quadruple |
| M.R. | 67 | F | Radiotherapy alkylating agents | 2 | Alopecia, nausea | Failure | 80 | 70 | Nil | Died 3 months after 2nd course, refused further treatment |
| G.K. | 64 | F | Radiotherapy Chlorambucil | 1 | Nil | Failure | 40 | 0 | Nil | Died 2 weeks after starting quadruple |
| M.N. | 65 | F | Radiotherapy | 1 | Nil | Failure | 40 | 0 | Nil | Died 2 weeks after starting quadruple |
| Cervical carcinoma | | | | | | | | |
| J.R. | 28 | F | Bone metastases | 1 | Alopecia | Failure | 20 | 0 | Nil | Died 2 weeks after starting quadruple |
| B.C. | 69 | F | Bone and supraclavicular nodes | 3 | Nil | Failure | 40 | 30 | Nil | Died 3 months after starting quadruple |
| W.P. | 60 | F | Pelvic recurrence | 3 | Nil | Failure | 60 | 60 | Nil | Alive. Quadruple discontinued after resection of deposit in small bowel |
| Testicular carcinoma | | | | | | | | |
| R.B. | 31 | M | Orchidectomy radiotherapy | 2 | Nil | Failure | 30 | 30 | Nil | Died 2 months after starting quadruple |
| C.S. | 27 | M | Orchidectomy radiotherapy | 2 | Nil | Failure | 30 | 0 | Nil | Died 1 month after starting quadruple |
| J.S. | 19 | M | Nil | 2 | Nausea | Failure | 70 | 70 | Nil | Alive, responding to Mithramycin |
| D.L. | 21 | M | Orchidectomy | 1 | Nil | Failure | 30 | 0 | Nil | Died 2 weeks after starting quadruple |
### Table IX.—Ten Cases of Malignant Melanoma

| Patient | Age | Sex | Site of metastases                          | Number of courses | Side effects | Objective | Karnofsky | Duration of response | Comment |
|---------|-----|-----|---------------------------------------------|-------------------|--------------|-----------|-----------|---------------------|---------|
| P.D.    | 54  | F   | Pleural deposits, local recurrence          | 2                 | Leucopenia   | Failure   | 40        | 40                  | Nil     |
| R.S.    | 42  | F   | Cutaneous lymph nodes, lungs                | 2                 | Leucopenia   | Failure   | 60        | 50                  | Died 6 months after starting quadruple |
| E.B.    | 39  | M   | Cervical nodes, liver                       | 1                 | Nil          | Failure   | 50        | 50                  | Nil     |
| R.K.    | 42  | M   | Small bowel, brain                          | 3                 | Alopecia, nausea | Failure | 70       | 70                  | Died 10 months after starting quadruple |
| J.W.    | 39  | M   | Small bowel, brain                          | 5                 | Leucopenia   | Failure   | 70        | 70                  | Died 10 months after starting quadruple due to cerebral haemorrhage |
| D.W.    | 27  | M   | Small bowel, liver, lungs                   | 4                 | Leucopenia   | Failure   | 70        | 60                  | Died 10 months after starting quadruple |
| E.P.    | 55  | F   | Bone, lungs                                 | 3                 | Nil          | Failure   | 50        | 50                  | 4 months after starting quadruple |
| V.P.    | 60  | F   | Local cutaneous recurrence                  | 2                 | Nil          | Failure   | 80        | 80                  | Alive following ablation of affected leg |
| S.E.    | 39  | F   | Local cutaneous recurrence, ovarian, retro-peritoneal nodes, liver | 2 | Nil | Failure | 50 | 70 | Died 3 months after starting quadruple |
| S.O.    | 40  | M   | Local cutaneous recurrence of lower limb    | 1                 | Nil          | Failure   | 70        | 70                  | Alive after ablation of limb |
| Patient  | Age | Sex | Diagnosis                      | Indication                                | Number of courses | Side effects | Objective | Pre- % | Post- % | Karnofsky | Duration of response (months) | Comment                                           |
|----------|-----|-----|--------------------------------|-------------------------------------------|-------------------|--------------|-----------|--------|--------|-----------|-----------------------------|---------------------------------------------------|
| S.P.     | 61  | F   | Leiomyosarcoma mesentry        | Disseminated local disease                | 2                 | Nil          | Failure   | 30     | 30     | Nil       |                             | Died 2 months after starting quadruple            |
| L.F.     | 66  | M   | Liposarcoma thigh              | Disseminated to soft tissue disease, lungs | 12                | Nil          | Partial   | 80     | 90     | 9         |                             | Alive with control of disease                     |
| B.       | 30  | M   | Fibrosarcoma in cervical tissue | Recurrent local disease                   | 6                 | Nil          | Partial   | 90     | 90     | 6         |                             | Alive                                             |
| R.W.     | 14  | M   | Alveolar rhabdomyosarcoma      | Disseminated disease, cutaneous, pancreas, mediastinal lymph nodes | 18                | Alopeicia leucopenia | Complete to partial | 30     | 90     | 20        |                             | Died from intestinal haemorrhage                  |
| B.H.     | 23  | M   | Rhabdomyosarcoma of thigh      | Residual disease after radiotherapy, Recurrent pneumothorax | 6                 | Alopeicia     | Partial   | 80     | 80     | 3         |                             | Alive, recent recurrent pleurodoesis               |
| O.E.     | 60  | F   | Retroperitoneal leiomyosarcoma | Local recurrence after surgery and radiotherapy | 2                 | Leucopenia    | Failure   | 50     | 20     | Nil       |                             | Died 1 month after starting quadruple            |
| Patient | Age | Sex | Diagnosis                          | Indication                   | Number of courses | Side effects | Objective | Karnofsky | Duration of response (months) | Comment                  |
|---------|-----|-----|------------------------------------|------------------------------|-------------------|--------------|-----------|-----------|-----------------------------|---------------------------|
| R.H.    | 68  | M   | Carcinoma of stomach              | Local recurrence gastrectomy | 7                 | Peripheral neuropathy | Complete  | 50        | 90             | 8            | Alive                    |
| O.C.    | 60  | M   | Carcinoma of stomach              | Cerebral metastases         | 2                 | Nil          | Partial   | 50        | 80             | 2            | Alive                    |
| B.S.    | 55  | F   | Squamous carcinoma of anorectal junction lymph nodes | Liver, supraclavicular lymph nodes | 6                | Nil          | Complete  | 80        | 100            | 6            | Alive                    |
| C.K.    | 47  | M   | Carcinoma of colon                | Local recurrence and liver  | 4                 | Peripheral neuropathy | Partial   | 60        | 60             | 3            | Alive                    |
| A.H.    | 77  | F   | Carcinoma of colon                | Local recurrence after palliative radiotherapy | 1             | Severe stomatitis, alopecia | Partial   | 60        | 60             | 1            | Changed to 5-flourouracil alone because of severe stomatitis |
TABLE XII.—Miscellaneous

| Patient | Age | Sex | Diagnosis                  | Indication                                                                 | Number of courses | Side effects | Objective | Karnofsky Pre- | Karnofsky Post- | Duration of response (months) | Comment                        |
|---------|-----|-----|----------------------------|----------------------------------------------------------------------------|------------------|--------------|-----------|----------------|----------------|-------------------------------|--------------------------------|
| A.A.    | 19  | M   | Nephroblastoma             | Lung metastases controlled for 4 months with actinomycin D               | 3                | Nil          | Failure   | 40             | 40             | Nil                           | Died 3 months after starting course |
| J.H.    | 31  | F   | Recurrent nephroblastoma   | Recurrence after 27 years                                               | 3                | Leucopenia   | Partial   | 50             | 80             | 3                             | Died 4 months after starting quadruple from marrow infiltration |
| C.P.    | 17  | F   | Hepatoma                   | Local recurrence after radical surgery, lungs, peritoneal                 | 4                | Leucopenia   | Failure   | 60             | 70             | Nil                           | Alive, drug changed to ICRF. 159 |
| K.H.    | 6   | M   | Osteosarcoma               | Lung metastases                                                         | 3                | Leucopenia   | Failure   | 40             | 30             | Nil                           | Died 3 months after starting quadruple |
| D.O.    | 11  | F   | Round cell sarcoma of femur| Lung metastases                                                         | 3                | Nil          | Failure   | 30             | 30             | Nil                           | Died 3 months after starting quadruple |
logical side effects are now a minor problem and in no patient was treatment discontinued for this reason.

The most consistent response was seen in carcinoma of the breast, where all patients responded in some degree. Regression was clinically complete in 6 out of 14 cases. As all these patients had undergone previous hormonal or cytotoxic treatment these results can be considered encouraging.

There were only 10 patients with head and neck cancer, but a remission in 8 cases compared well with the report of Leone et al. (1968), and considerably better than the results of intra-arterial chemotherapy at this Centre.

Fourteen cases of carcinoma of bronchus were treated and 8 underwent brief remission (3 months or less). It is recognised that it is difficult to palliate bronchial carcinoma with cytotoxic agents and the use of quadruple chemotherapy in this small series is not encouraging.

Surprisingly no remissions were achieved with carcinoma of the ovary cervix or testicle.

The success claimed by Constanzi and Coltman (1969) was not confirmed in this series of melanomas, and we no longer treat this tumour with the quadruple regime.

In a small group of 6 soft tissue sarcomata only 1 failed to respond. If in a larger series this response rate were to be maintained it would be an improvement on previous experience (Newton, 1967; Wiltshaw, 1967).

In the small group of gastro-intestinal cancers, 4 out of 5 cases of carcinoma of the large bowel and stomach responded, and it is felt that where 5-fluorouracil has failed, quadruple chemotherapy may be of value.

Table XIII.—Response of Different Groups of Solid Tumours to the Modified Quadruple Regime

| Good remission | Moderate remission | No remission |
|----------------|-------------------|-------------|
| Breast carcinoma | Head and neck carcinoma | Malignant melanoma |
| Soft tissue sarcoma | Cervical carcinoma | Ovarian carcinoma |
| Bronchial carcinoma | Stomach and large bowel carcinoma | Testicular carcinoma |

Bone sarcoma

Table XIII summarises the value of this modified quadruple regime in the different groups of solid tumours.

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