during 1961–5 in the densely populated areas of Birmingham, Glasgow, and Manchester. Adequate precautions taken during the handling of cylinders, both at the time of distribution and before use, can ensure safety in the use of 50/50% nitrous oxide and oxygen mixture.

We are indebted to the British Oxygen Company for supplying the Entonox demand-valve and a generous supply of cylinders. We are also indebted to the Meteorological Office, whose records provided the basis for Table II.

REFERENCES

- Cole, P. V. (1964). *Anaesthesia*, 19, 3.
 — and Nainby-Luxmore, R. C. (1962). *Ibid.*, 17, 505.
 Gale, C. W., Tunstall, M. E., and Wilton-Davies, C. C. (1964). *Brit. med. J.*, 1, 732.
 Hill, D. W., Hook, J. R., and Bell, E. G. (1961). *J. sci. Instrum.*, 38, 100.
Lancet, 1965, 1, 1229.
 Moir, D. D., and Bisset, W. I. K. (1965). *J. Obstet. Gynaec. Brit. Cwlth.*, 72, 264.
 Nainby-Luxmore, R. C. (1964). *Anaesthesia*, 19, 421.
 Tunstall, M. E. (1961). *Lancet*, 2, 964.
 — (1963). *Brit. med. J.*, 2, 915.

Methotrexate in Treatment of Sarcomata

E. WILTSHAW,* M.B., B.CH.

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Chemotherapeutic agents are so commonly used in the treatment of widespread malignant disease that it is unlikely that any tumour has escaped a trial of cytotoxic drugs. However, in some of the rarer tumours, including the connective-tissue sarcomata, no proper assessment of the value of chemotherapy can be made, because reports are based on the treatment of a few or even single cases. In 1960 we treated a patient suffering from fibrosarcoma of the bladder with a combination of chlorambucil, methotrexate, and one dose of actinomycin D (Case 1). The regression which followed was dramatic; but the toxic manifestations were severe: some features of this response suggested that methotrexate was the effective agent. Subsequently, therefore, patients suffering from soft-tissue sarcomata beyond the scope of surgery or radiotherapy were treated with methotrexate. This paper reports the results in leiomyosarcoma, fibrosarcoma, and undifferentiated sarcoma.

Patients Treated

Between 1 March 1960 and 30 September 1965 32 patients were treated. There were 15 cases of leiomyosarcoma, eight of fibrosarcoma, and nine of undifferentiated sarcoma.

The effect of chemotherapy could not be assessed in seven cases. One patient had no palpable tumour when treatment was begun, though a fibrosarcoma had been found during operation and was only partially removed. Three patients were lost to follow-up (two cases of leiomyosarcoma and one of undifferentiated sarcoma). Finally, three patients died within 14 days of starting chemotherapy (two cases of leiomyosarcoma and one of undifferentiated sarcoma). The results in the remaining 25 patients are reported here (see Table I).

Three patients were treated for inoperable primary tumours, 16 for local recurrence of tumour with or without metastases, and six for generalized disease but with no local recurrence. Histological specimens were reviewed in all the cases.

Method of Treatment

All the patients received methotrexate orally. Intravenous injections were also given if the patient was vomiting or there were doubts about absorption of the drug. From 2.5 to 10 mg. was given daily in divided doses by mouth for 2 to 15 days. One patient (Case 9) had a single oral course of 5 mg. daily for 45 days. This patient also received an intra-arterial infusion. The remaining patients received 2 to 29 courses.

The daily dose and the duration of each course of drug were regulated according to the side-effects produced and were not calculated on the basis of body weight. Commonly, five-day courses were planned at 10 mg. daily, but were often cut short by soreness of the mouth, frank ulceration, nausea or vomiting, and occasionally by leucopenia. The next course was begun when the toxic effects had disappeared, or within six weeks. The time between courses varied from four days to six weeks (commonly every two weeks), and courses were given less frequently as the patient improved. Intra-arterial and intravenous therapy were given by continuous infusion over a period of 8 to 24 hours in doses of 10 to 25 mg. daily until evidence of toxicity appeared. This took two to three days in the case of intravenous infusions, and five days in the one case of intra-arterial infusion.

Side-effects and Toxicity

Anorexia was a common side-effect (11 patients) and tended to be more troublesome during successive courses. Two of the 11 patients vomited at the end of each course of methotrexate. Oral ulceration was seen in 18 cases; it occurred at the end of a course, or in the three days after the last dose of the drug. Six did not have ulceration, and one had so much tumour in the mouth that other oral lesions could not be recognized. Though five-day courses of therapy were planned, many patients could not tolerate more than three days' treatment, and a few could accept only two-day courses of 5 to 10 mg. The duration of the courses and the daily dose of the drug were regulated for each patient so that he had as few side-effects as possible. The first symptom of oral toxicity was a slight soreness in the mouth, usually on the inner side of the lips or tongue. The earliest sign was a local erythema of the mucous membrane. Frank ulceration would often develop in this area within 24 hours.

The effect of methotrexate on the peripheral blood was sometimes severe and rapid. The effect on the blood count was recorded as "severe" if the haemoglobin concentration fell 3 g./100 ml. or more, if the total leucocyte count fell by 50% or more, and the platelet count fell by 50% or more after the first course of the drug. A severe fall in the haemoglobin was seen in 10 cases, of the white cell count in 15, and of the platelet count in eight. The effect on the peripheral blood was usually less with successive courses of therapy, but in one instance a single intravenous dose of methotrexate in a patient with severe renal damage caused marrow aplasia and death. The only other side-effect of treatment was mild partial alopecia in two patients.

* Chester Beatty Research Institute, London S.W.3.

Results

Tumour regression in varying degree was observed in 13 cases (Fig. 1). In five it was transient and involved only some of the tumour deposits. The response in these cases is referred to as "transient regression." In eight cases all known deposits of tumour regressed, sometimes completely, and the patients' general condition improved considerably for two or more months—in one case up to 45 months. The response in these cases is referred to as "remission." Of the five patients who had a transient regression there was some decrease in the size of lung deposits in two cases (Cases 12 and 21), dramatic regression in the size of a local recurrence in the thigh in two (Cases 6 and 7), and in one (Case 2) an extremely rapidly growing recurrent oral fibrosarcoma did not increase further in size during the 14 days of methotrexate therapy. This patient was very ill when chemotherapy was started, and because of severe marrow toxicity treatment had to be stopped. The tumour again grew rapidly and the patient died eight days later. When regression occurred reduction in the size of the tumours was usually seen to begin between three and six weeks from the start of treatment, sometimes after one week, and occasionally not for as long as 12 weeks. Remissions lasted 2, 4, 6, and 36 months in the patients who died, and four patients were alive 3, 10, 28, and 45 months after methotrexate treatment began.

Response Related to Histological Type and Origin of Tumour

A response was recorded in five of the seven patients with fibrosarcoma (transient regression in three, and two remissions), in four of the seven with undifferentiated sarcoma (transient regression in one, and three remissions), and in 4 of the 11 patients with leiomyosarcoma (transient regression in one, and three remissions). The regressions in leiomyosarcoma occurred in primary or locally recurrent tumour except for a transient regression in one case with lung metastases.

FIG. 1.—Principal features of the disease and its course in 25 cases of sarcoma treated with methotrexate.

Most of the tumours arose in the uterus (six definitely and three probably) and in the leg (seven) (Table I). Two arose from the bladder and one each from the parotid, the diaphragm, the breast, the ovary, and the jaw. One other probably originated in the thymus, and in one case the origin was not known. Four remissions were obtained in the nine tumours originating in the uterus and one transient regression; in the seven leg tumours there were three transient regressions, and one remission. The breast tumour and both of the bladder tumours remitted. Transient regression was also recorded in the jaw tumour.

TALBE I.—Histological Type and Probable Origin of 25 Cases of Sarcoma Treated with Methotrexate

Histology	No.	Origin	No.
Leiomyosarcoma	11	Uterus	7
		Bladder	1
		Leg	2
		Other	1
Fibrosarcoma	7	Leg	3
		Bladder	1
		Other	3
Undifferentiated	7	Uterus	2
		Leg	2
		Other	3

Response and Toxicity

In all patients courses of the drug were continued until toxicity was apparent, or, if the patient remitted, until the disease was evidently progressing again. Eighteen of the 25 patients had mild to severe oral ulceration: the tumours in 11 of these did not respond to treatment, two had transient regressions, while five remitted. In six patients oral toxicity was not seen and in one other patient oral toxicity could not be assessed; two did not respond, three had transient regressions, and two remitted. The effect of methotrexate on the peripheral blood count varied greatly, not only from patient to patient but at different times in the course of a single patient's illness. However, it was clear that regression and remission could occur in the absence of toxic marrow manifestations. On the other hand, the deliberate production of toxic manifestation in the hope of causing regression of the resistant tumours was not effective (Table II). Serum folate levels were estimated before therapy in 10 patients. They ranged from 3 to 6.4 $\mu\text{mg./ml.}$ Seven patients had concentrations of 4 $\mu\text{mg./ml.}$ or less, but the marrow toxicity was no greater in these than in three patients with more than 4 $\mu\text{mg./ml.}$ Falls in the haemoglobin concentration and neutrophil and leucocyte counts were more common in the fibrosarcoma group. These patients did not, however, suffer more from oral ulceration.

TALBE II.—Effect of First Course of Methotrexate on Total Leucocytes, Platelet Count, and Haemoglobin Level Related to Histology and Regression of the Tumours

Histology	Severe Effects on Elements of Peripheral Blood		
	Leucocytes	Platelets	Hb
Leiomyosarcoma	5/11	3/11	3/11
Fibrosarcoma	5/7	4/6*	6/7
Undifferentiated	5/7	1/7	1/5*
Regression†	9/13	5/13	6/12*
No regression	6/12	3/11*	4/11*

* In some cases not enough counts were done to record the lowest probable fall in each element.

† Including cases with transient regression only.

Radiotherapy and Response

Leiomyosarcoma, fibrosarcoma, and undifferentiated mesenchymal sarcoma are relatively radioresistant, but because occasional patients do respond and there is no other effective method of treatment many patients are still given radiotherapy.

Radiotherapy was given to 17 of the patients in this series. One was treated postoperatively and benefit could not be assessed; two others were treated unsuccessfully for painful lesions in bones; while of 14 masses which were treated, one regressed completely, four slightly, and nine did not respond. Of the five patients whose tumours showed transient regression after methotrexate three had been irradiated before chemo-

free tissue. This in part accounts for the high rate of local recurrence. Local recurrences may still be cured by radical surgery, but most patients develop metastases (Lieberman and Ackerman, 1954; Stout and Hill, 1958; Aaro and Dockerty, 1959; Spiro and Koss, 1965; van der Werf-Messing and van Unnik, 1965). Metastases from fibrosarcoma may appear up to 15 years after removal of the primary tumour; the five-year

FIG. 2.—Case 8. Effect of methotrexate on the blood picture and on the tumour in a woman aged 56 with undifferentiated sarcoma of uterus. When first treated she had a mass in the pelvis, a non-functioning right kidney, and multiple deposits in right lung and mediastinum as well as a pleural effusion. The pelvic mass disappeared after radiotherapy, while the kidney function returned and the chest deposits disappeared after methotrexate was given. A lapse of treatment for a few weeks resulted in regrowth of lung deposits, which regressed again completely when methotrexate was reinstituted. A further tumour appeared in 1963 and did not respond to treatment with methotrexate, chlorambucil, or radiotherapy.

therapy was given; one of these had insignificant regression of the tumour. Of the eight patients who remitted after methotrexate six had been irradiated before receiving chemotherapy. The regression after irradiation was complete in one case, slight in two others, negligible in two, and could not be assessed in one.

Discussion

Some cases of primary leiomyosarcoma and fibrosarcoma can be cured by wide local excision of the tumour. Because wide excision often involves a very mutilating operation, many surgeons include only a small margin of apparently tumour-

follow-up method is therefore inadequate for assessing the cure rate. Van der Werf-Messing and van Unnik have shown that when metastases do occur survival may still be prolonged, and some patients have lived as long as 15 years after their appearance. Patients with leiomyosarcoma do not live as long after the development of metastases, but it is not true that survival for more than one year is unusual. Spiro and Koss reported six patients, in a series of 24, who survived 16 to 36 months, and in our series two patients (Cases 18 and 25) survived 14 and 19 months, though they did not respond to treatment.

When the removal of the primary tumour or of a local recurrence is not practicable radiotherapy is often given, but with limited success (Stout, 1948; Aaro and Dockerty, 1959; Berg and McNeer, 1960; Spiro and Koss, 1965). Multiple deposits have hitherto been regarded as untreatable, though several chemotherapeutic agents have been tried. Molander (1966) treated 23 patients with chemotherapy and radiotherapy with some good results, including responses in two fibrosarcomas, a leiomyosarcoma, and a spindle-cell sarcoma. He used three chemotherapeutic agents in combination: actinomycin D, methotrexate, and cyclophosphamide.

The series of patients reported here shows that methotrexate can produce worth-while regressions in some 30% of cases. Some patients had dramatic complete regression of large amounts of tumour; in one (Case 8, Fig. 2) multiple masses due to undifferentiated sarcoma in the lung regressed completely for 18 months. Another patient (Case 16, Fig. 3) with an enormous leiomyosarcoma of the bladder had very rapid regression of his mass. He died from a combination of drug toxicity and renal damage due to his tumour, but at necropsy it was clear that the shrunken tumour would have been resectable.

Sometimes the effects of the drug were less easily interpreted. One patient with leiomyosarcoma of the uterus (Case 17) had a recurrent mass in the left iliac fossa with a left hydronephrosis. After methotrexate therapy the hydronephrosis had disappeared but the mass remained. This mass appeared after a course of radiotherapy to the pelvic area; it was irradiated again but did

FIG. 3.—Case 16. Effect of methotrexate on the blood count, blood urea, and blood pressure in a man aged 48 with leiomyosarcoma of bladder and chronic renal failure. The tumour regressed continuously, but the patient was unable to excrete the drug efficiently and he died of methotrexate toxicity.

not regress. Clinically this mass could have been due in part to irradiation fibrosis and in part to oedema of the tissues. At the time of writing there was no definite evidence that tumour was present in this area.

Five of the eight patients who remitted have relapsed, and a sixth (Case 16) died from the toxic effects of methotrexate while the tumour was still regressing. In one patient who relapsed (Case 8) the original metastases did not reappear, and a single apparently resistant tumour in the lung caused her death. This was the only tumour found at necropsy, though she had had at least three other tumours in the lung, and probably one in the pelvis, when treatment was begun. In another case (Case 3) multiple subcutaneous tumours all regressed. Later one recurred and grew rapidly while chemotherapy was still being given. Biopsy of this mass showed it to be of similar histology to other biopsied metastases.

In fibrosarcoma and undifferentiated sarcoma regressions were observed in primary tumours, local recurrences, and distant metastases. In leiomyosarcoma, however, regressions were observed in three out of five primary tumours or local recurrences, but in only one out of six cases with metastases.

In such a heterogeneous group of patients the rate of growth of the tumour was very difficult to measure. It was assessed first from the duration of symptoms prior to diagnosis, and second from the duration of the apparently tumour-free period between the original excision and recurrence. The latter measurement could be made in only 16 patients because in three cases the primary tumour was never removed and metastases were present in six at the time of diagnosis.

There were eight patients whose symptoms were present six months or more before the diagnosis was made. One had a transient regression and two remitted (see Fig. 1). Despite the variable sites of origin of the tumours the diagnosis was made within six months of the first symptom in six out of seven of the fibrosarcomas and within 12 months in all of the leiomyosarcomas. The histologically undifferentiated sarcomas either had a long history (three out of seven had symptoms for more than 12 months) or a very short one (three out of seven had symptoms for less than two months) before diagnosis. Measurement of the time interval between diagnosis and recurrence was possible in 16 cases. Five patients had a "disease-free period" of more than 12 months. There were two remissions in this group. Of the 11 patients who had a "disease-free period" of less than 12 months three remitted. Thus it was not possible to relate the response to methotrexate to the rate of growth of the tumour.

Though 17 patients, including 9 of the 13 who later showed regression with methotrexate, received external irradiation, only one had complete regression after radiotherapy. All were irradiated before the drug was given, but regression could not be attributed in any case to the radiotherapy. Thus the sensitivity to methotrexate is independent of radiosensitivity.

Toxic effects on the buccal mucosa were seen in most of the patients, and were in fact more common in those patients who did not respond to therapy, because treatment was continued until signs of toxicity developed. Falls in the leucocyte and platelet counts and in the haemoglobin levels were common, particularly in the early courses of therapy, but, again, severe falls were as frequent in the patients who did not show regres-

sion as in those who did. In the cases of fibrosarcoma severe falls in the peripheral blood elements occurred more often than in the cases of leiomyosarcoma and undifferentiated sarcoma. However, oral ulceration occurred just as often. It was thought possible that the increased susceptibility to the toxic effects of methotrexate in fibrosarcoma might be due to folate utilization by the tumour, but there was no correlation between the tumour size in the fibrosarcoma patients and the effect on the blood. The serum folate levels before treatment in three cases were 6.4, 4.0, and 4.5 $\mu\text{mg./ml.}$ These were not lower than the average for the whole group.

Response to methotrexate could not be related to the site of origin of tumour, nor, perhaps, to its rate of growth, but there was some relation to the histological type in that metastases from leiomyosarcoma very rarely regressed. Since this series was closed five patients with liposarcoma have been treated with methotrexate and none has responded.

Because some of the patients had rapid falls in their leucocyte counts frequent blood counts are necessary, and an assessment of renal function is essential before treatment is begun. However, it is not necessary to produce severe toxicity in order to achieve regression, and when remission occurs regression is usually rapid and unequivocal, while gain in weight and symptomatic improvement can be dramatic.

Summary

Methotrexate was given to 11 patients with leiomyosarcoma, seven with fibrosarcoma, and seven with undifferentiated sarcoma. There were eight worth-while remissions—three of leiomyosarcoma, two of fibrosarcoma, and three of undifferentiated sarcoma. Methotrexate was usually given by mouth in doses ranging from 2.5 to 10 mg. daily in courses lasting from 2 to 15 days. Oral and bone-marrow toxicity occurred, but neither was necessary in order to achieve a remission. The sensitivity of these tumours to methotrexate is independent of radiosensitivity.

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REFERENCES

- Aaro, L. A., and Dockerty, M. B. (1959). *Amer. J. Obstet. Gynec.*, **77**, 1187.
- Berg, J., and McNeer, G. (1960). *Cancer (Philad.)*, **13**, 25.
- Lieberman, Z., and Ackerman, L. V. (1954). *Surgery*, **35**, 350.
- Molander, D. W. (1966). *Amer. J. Roentgenol.*, **96**, 150.
- Spiro, R. H., and Koss, L. G. (1965). *Cancer (Philad.)*, **18**, 571.
- Stout, A. P. (1948). *Ibid.*, **1**, 30.
- and Hill, W. T. (1958). *Ibid.*, **11**, 844.
- van der Werf-Messing, B., and van Unnik, J. A. M. (1965). *Ibid.*, **18**, 1113.