(1) The technique of therapeutic lymphography is occasionally difficult. In some cases it may be necessary to give multiple injections in order to fill nodes adequately, which can be difficult for the occasional operator.
(2) Distribution of the isotope in the node is not always homogeneous, a condition essential for complete destruction of metastases. Other isotopes such as radioactive yttrium, with a longer range β-particle, or a combination of different isotopes may obviate the occasional patchy distribution.

More work is needed in these aspects of endolymphatic treatment, and this must be done in specialized centres.

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Perfusion in Limb Melanoma: Indications and Results

Approximately 500 people in England and Wales die each year of malignant melanoma. Treatment by chemotherapeutic limb perfusion (Ryan *et al.* 1957, Creech *et al.* 1958) subsequent to wide excision and grafting with or without block dissection is widely practised in North America, but there are no longterm results published of such treatment in this country. This paper analyses experiences with this therapy in the Surgical Unit at St Mary's Hospital where, for the last thirteen years, it has been used for patients with malignant melanoma.

Method

The affected limb is isolated by a tourniquet and the main artery and vein are cannulated. An extracorporeal circuit containing a pump oxygenator is used. The cytotoxic agent used is 1-phenylaline nitrogen mustard in a dose of 1–2 mg/kg body weight in divided doses over 40–105 min. A crude estimate of the systemic leak of the drug is obtained by using a radioactive tracer in the perfusion circuit. Block dissection is then performed where indicated.

Clinical Material

Patients were selected for perfusion if the primary lesion was invasive, using the histological classification of Lloyd (1962), and if full investigation had indicated that the primary or recurrent tumour was confined to one limb. There were 56 patients in all, 14 men and 42 women; 50 underwent one perfusion, 5 patients had 2, and 1 had 3. They were grouped as follows: (1) Primary invasive melanoma treated by wide excision and grafting, perfusion and bloc dissection. (2) Recurrent melanoma treated by wide excision, grafting and perfusion. (3) Recurrent melanoma treated by perfusion alone because of extensive local disease.

Complications

The complications of the operation are summarized in Table 1. The thrombosed femoral artery was diagnosed at the time of the second perfusion, ten months after the initial treatment; short occlusion was found but peripheral pulses were present and there was no history of claudication. The incidence of local wound complications has been reduced in the last 13 patients by using a medially based skin flap when performing bloc dissection. The neuritis and vasomotor changes in the hand were in the same patient and recovery was complete. Leukopenia was defined as a drop in white cells below 4000/mm^3; these 3 patients were treated in an isolation ward and did not develop any infections.

Results

Of the 56 patients perfused, 43 were available for a five-year survey. Of these 43, 29 patients survived five years, giving an overall figure of 67% (36 women and 7 men). Results in our three groups were as follows:

Group 1: Of 16 patients with primary invasive limb melanoma, 11 survived five years. Twelve patients had inguinal or axillary nodes free of

Table 1

Complications following surgery, perfusion and chemotherapy in 56 patients with malignant melanoma

Complications	*No. of cases*
Surgery	
Sloughed groin flaps	9
Lymphœdemas	6
Lymph cysts	5
Infected wounds	3
Chest infections	2
Regraft	1
Perfusion	
Thrombosed femoral artery	1
Deep venous thromboses	2
Neuritis in the hand	1
Vasomotor changes in the hand	1
Chemotherapy	
Leukopenias	3

tumour histologically and 9 of these survived five years (7 tumour free at over six years). Four had positive nodes and 3 of these survived five years (1 tumour free at six years).

Group 2: Of 14 patients with localized recurrence treated by excision and grafting plus perfusion, 11 survived over five years. Negative inguinal or axillary nodes were found in 9 patients, all of whom survived five years; 1 patient had 2 perfusions. Of the 5 patients with positive nodes, 2 survived five years.

Group 3: Of 13 patients treated with perfusion alone, 7 lived five years, 4 of whom had more than one perfusion. Of the remaining 6 patients, 4 had a short response and 2 had no response.

Discussion

These results compare well with those of Heise *et al.* (1961) who, in a five-year survey of 1447 patients with limb melanoma who had undergone all forms of treatment, reported an overall survival of 51.5%. McBride & Clark (1971), reviewing 240 patients following perfusion, concluded that there was a 10% increase in five-year survival compared with conventional treatment; local recurrence, skin grafting and amputation were also reduced. Krementz & Ryan (1972), reporting 14 years experience with perfusion for invasive limb melanoma, showed that of 108 patients with Stage 1 melanoma, 87 were disease free at five years, and of the 119 patients with Stage 2 melanoma, 50 were disease free at five years.

Conclusion

Although this series is small the following points can be made. Regional perfusion for melanoma is a relatively safe procedure in suitable centres, there was no loss of limbs and no deaths in this series. Our results, supported with other series, indicate that regional perfusion probably does offer patients increased survival to five years with a long tumour-free interval. Patients with extensive limb melanoma which could be excised and grafted at the expense of lymphœdema and possible ulceration with severe cellulitis often have a response to perfusion, like those patients with inoperable limb disease, which may be prolonged. Amputation in this situation may be avoided.

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Investigational Drugs for the Treatment of Malignant Melanoma

Treatment of malignant melanomas by chemotherapy is unsatisfactory. Even with the best drugs, used as single agents, some 80% of patients show no response. Such successes as have been claimed, most in non-randomized, uncontrolled clinical evaluation studies, have to be judged against the very variable clinical course that this malignancy may take. Even without treatment, some nodules may regress, whilst other nodules grow vigorously. The published literature therefore probably reflects a response rate which errs on the optimistic (Table 1). Studies in which few or no objective regressions are obtained are also less likely to be reported.

Actinomycin D is claimed to give an objective response rate of 33%; though it must be asked at what toxic cost, how long were regressions maintained, how complete were they and how much clinical benefit did patients obtain. In any tabulation of anticancer drugs the answers to these questions ought to be built into their ranking.

It seems curious that so few cases treated with cyclophosphamide, an agent about which so much is known, have been reported; particularly as it appears to have given reasonable results. If one can judge from the few cases that have been reported, low doses (7.5 mg/kg i.v. per day for 6 days and then 10 mg/kg per week) are as effective as high single doses of 100 mg/kg i.v. repeated every three weeks.

DTIC or 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide has been very widely tested in the last three years, particularly in the United States. It appears to be an antimetabolite competitive with 5-aminoimmidazole-4-carboxamide, a precursor in *de novo* synthesis of purine. In addition, it also behaves as an alkylating agent. Its exact mechanism of action is uncertain.

There is a striking consistency of approximately 20% in the response rate, in individual reports (Carter & Friedman 1972). This is somewhat unusual, but probably indicates a true and direct activity on the tumour. Where responses are very variable, as for example those given for actinomycin D and hydroxyurea where responses have been as low as zero, it is probable that variable blood levels may be as much responsible as variable responses by the melanoma cells to the drug involved.

Because of erratic oral absorption (Loo *et al.* 1968) DTIC can only be given intravenously.