PAPERS AND ORIGINALS

Clinical Effects of Whole-body Hyperthermia in Advanced Malignancy

R. T. PETTIGREW, JEAN M. GALT, C. M. LUDGATE, A. N. SMITH

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Summary

Fifty-one patients in the terminal stages of cancer have been treated with whole-body hyperthermia either alone (38 cases) or in combination with chemotherapy (13 cases). Altogether 227 treatment sessions were held averaging four hours each. The most sensitive tumours were those of the gastrointestinal tract and sarcomas. Breast and genitourinary tumours did not respond, and lung tumours and melanomas were only partially responsive. Major complications were remarkably few.

Introduction

Temperatures in the range of 41 to 42°C have been shown to be lethal to tumour cells but not damaging to normal cells (Cavaliere *et al.*, 1967; Vermel and Kuznetsova, 1970; Obergaard and Overgaard, 1972). Hyperthermia has been applied to human tumours in vivo by isolated limb perfusion, either alone or in combination with cytotoxic drugs (Cavaliere *et al.*, 1967; Stehlin, 1969), by whole-body hyperthermia (Warren, 1935; Henderson and Pettigrew, 1971), and by local irrigation (Hall *et al.*, 1974). This paper records the clinical responses of a series of patients to whole-body hyperthermia either alone (38 patients) or in combination with cytotoxic therapy (13 patients). All the patients were in the terminal stages of their disease and unsuited to further treatment by conventional methods.

Method

The method used was that described previously (Pettigrew *et al.*, 1974), in which the narcotized patient is covered with molten wax at 50°C to prevent evaporation of sweat and insulate the body. The overall effect is to raise the body temperature by 3 to 6° an hour depending on body weight. Previous work has shown that the method is safe for treatment periods up to eight hours provided that the temperature does not exceed 41·8°C and so long as there is adequate replacement of the water and salt lost in the sweat (Pettigrew *et al.*, 1974).

Thirty-eight patients have been treated with hyperthermia alone in 188 treatment sessions and a further 13 with hyperthermia in combination with cytotoxic drugs. In the first group the average length of each treatment above 41°C was four hours, and treatments were given at weekly intervals. In the second group treatment was given in three sessions each separated by three days. The first lasted 90 minutes and the other two four hours. Cytotoxic drugs were given by intravenous bolus injection during the last treatment. Patients with malignant melanoma were given Melphalan 1 mg/kg; the others were given cyclophosphamide 200 mg during the period of temperature rise and fluorouracil 15 mg/kg and vincristine 1 mg at a temperature of 41°C.

The response to treatment was judged favourable if there was weight gain or pain relief plus either regression in tumour size on direct measurement or pathological evidence of necrosis in serial biopsy specimens or radiological evidence of regression. Further evidence of heat-induced tumour necrosis was obtained at necropsy in five of the six patients who died soon after hyperthermia.

Nineteen patients were excluded from the series. Fourteen were treated in the developmental stages of the method when temperatures above 40°C were not routinely used. These patients did not respond, and it is now accepted that temperatures in excess of 41°C are needed (Giovanella *et al.*, 1970). A further five patients with no obviously measurable tumours were treated for symptomatic relief of pain only.

Results

HYPERTHERMIA ALONE

Though the numbers were small tumours of gastrointestinal origin and sarcomas appeared to respond more than genitourinary or breast neoplasms; lung tumours and malignant melanomas showed an intermediate response (table I).

Western General Hospital, Edinburgh, EH4 2XU
R. T. PETTIGREW, M.B., F.F.A. R.C.S., Consultant Anaesthetist
C. M. LUDGATE, M.B., F.R.C.S., Surgical Registrar

University of Edinburgh
A. N. SMITH, M.D., F.R.C.S., Reader in Clinical Surgery
JEAN M. GALT, B.SC., Research Associate

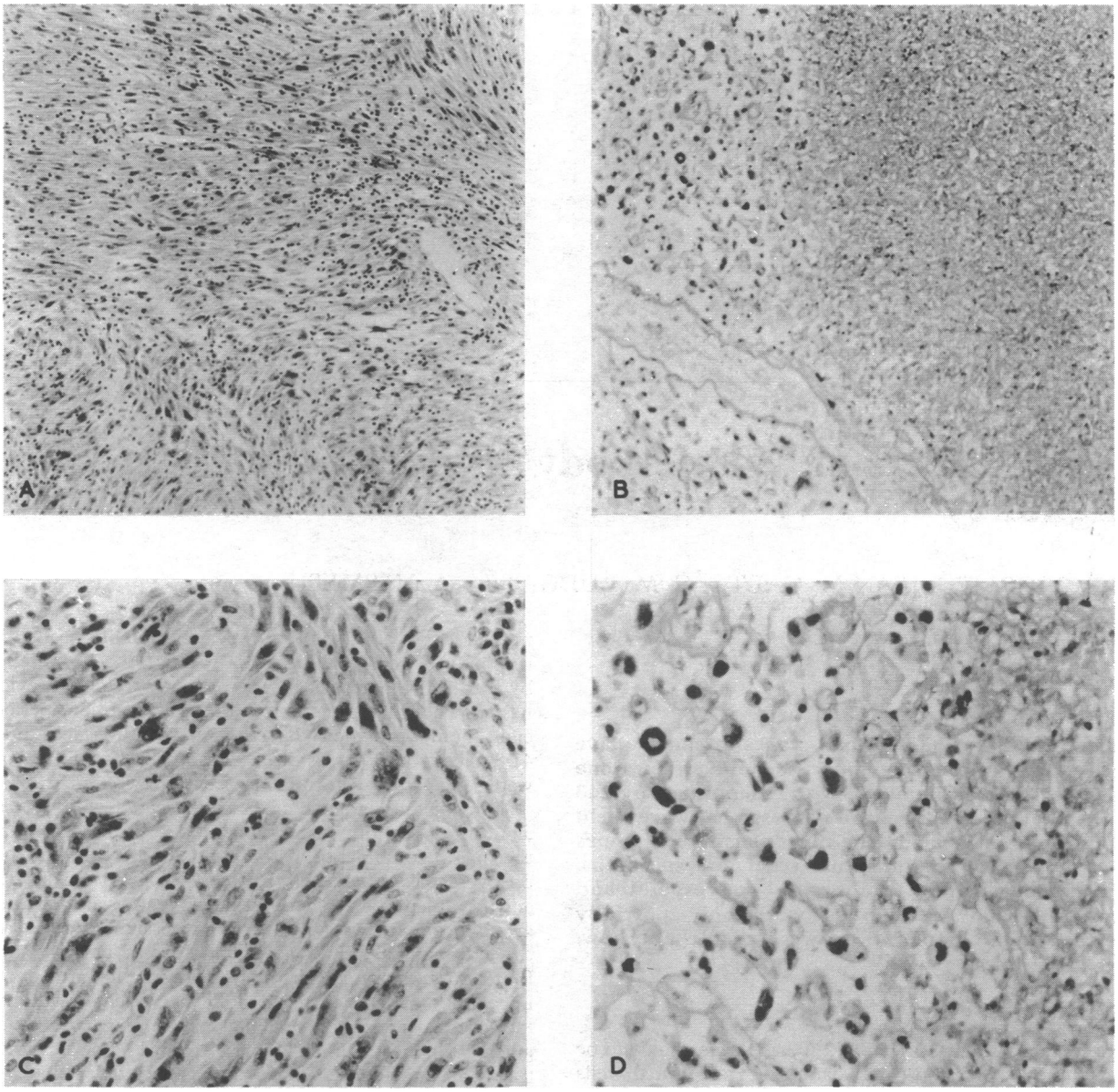

FIG. 1—Photomicrographs of liposarcoma. A and C, appearances of primary tumour after resection. (Haematoxylin and eosin. A × 110. C × 270). B and D, appearances of recurrent tumour four months later after treatment with hyperthermia showing total necrosis to right side and degenerate cells at left margin. (Haematoxylin and eosin. B × 110. D × 270).

Case Reports

Sarcoma.—Eight cases. In one patient a lung deposit disappeared, a second showed healing of pathological fractures, and a third showed complete regression of a fibrosarcoma recurrent in the operation scar. A fourth had a hindquarter amputation for osteogenic sarcoma; two months after the end of an 18-month course of treatments the tumour recurred in a heat-resistant form. A fifth patient, with an alvanced liposarcoma, died 24 hours after treatment. Necropsy showed recent massive necrosis throughout the tumour (fig. 1). Two had subjective improvement with pain relief, and a child with rhabdomyosarcoma showed no response.

Carcinoma of Stomach.—Three cases. Two anorexic patients who had been in great pain gained weight and were able to lead a relatively normal life. The third had extensive mediastinal and lung metastases and died 48 hours after treatment. At necropsy

TABLE I—*Results of Treatment with Hyperthermia Alone*

Tumour Type	No. of Patients Treated	Previous Treatment			Objective Responses	Subjective Response	No Response	Survival from Start of Thermotherapy (Weeks)
		Surgery	Radiotherapy	Chemotherapy				
Sarcoma	8	6	4	2	3+1*	6	1	84, 52, 20, 8, 4, 2, 1, 0·14
Gastric Carcinoma	3	3	0	1	2+1*	2	0	16, 16, 0·28
Carcinoma colon ..	4	4	0	1	2	2	2	20, 8, 4, 0·71
Melanoma	7	7	2	2	3	4	3	12, 12, 8, 8, 4, 4, 3
Carcinoma lung ..	3	0	3	0	2	3	0	24, 20, 4
Carcinoma breast ..	2	2	2	1	0	1	1	12, 12
Ovarian carcinoma, teratoma testes	4	4	2	3	0	0	4	24, 16, 8, 4
Neuroblastoma, nephroblastoma	3	3	3	3	1+2*	1	0	24, 0·85, 0·28
Miscellaneous ..	4	2	4	4	1	1	2	32, 24, 12, 0·57

* Necropsy evidence of recent tumour necrosis.

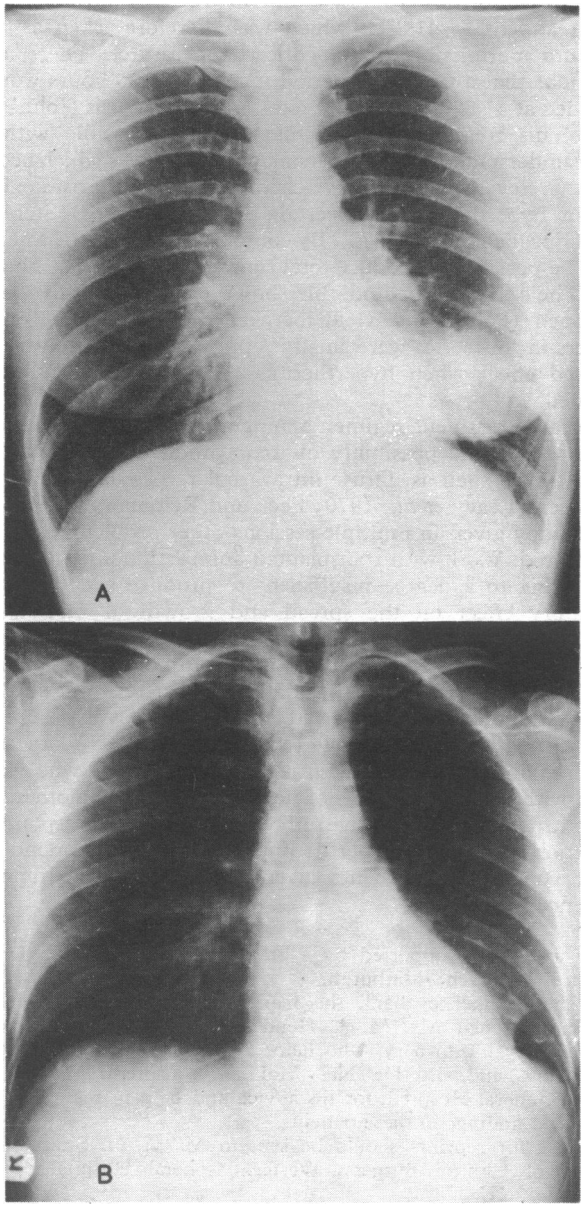

FIG. 2—Chest x-ray pictures from patient with bronchogenic carcinoma. A, appearances before treatment with hyperthermia. B, appearances six weeks later after six treatment sessions.

there was extensive necrosis of the tumour causing compression of the bronchus.

Carcinoma of Colon.—Four cases. One patient had almost complete regression of massive hepatomegaly; a second had regression of skin nodules on the lower abdomen. The other two cases showed no response.

Malignant Melanoma.—Seven cases. In three cases there was good initial regression of secondary deposits and pain relief. One patient had pain relief alone and three showed no response.

Carcinoma of Lung.—Three cases of bronchogenic carcinoma. In one patient with adenocarcinoma there was regression of the primary lung tumour (confirmed at necropsy) (fig. 2) though the secondary deposits remained active. The second patient, with a squamous carcinoma, showed regression of a secondary deposit in the lumbar spine, and the third had relief from pain but showed no tumour regression.

Breast Cancer.—Two patients with scirrhous carcinomas were treated, one obtaining pain relief alone.

Ovarian and Testicular Tumours.—Two testicular teratomas and two ovarian papillary tumours showed no response to treatment.

Neuroblastoma and Nephroblastoma.—Two children with neuroblastomas were treated. One showed a good initial response, with healing of ulcerated skin over the tumour in his jaw. The second showed initial improvement till he developed respiratory difficulties and died two days after treatment. Necropsy showed multiple haemorrhagic areas of necrosis in the tumour. One child with a nephroblastoma showed initial improvement but also died from a respiratory arrest. At necropsy there was gross necrosis of the tumour.

Miscellaneous Tumours.—One case of mycosis fungoides showed initial healing and there was pain relief alone in a case of adenocarcinoma of the nasopharynx. One case each of chronic myeloid leukaemia and transitional cell carcinoma of the bladder showed no response.

HYPERTHERMIA IN COMBINATION WITH CYTOTOXIC THERAPY

The results in the 13 patients given cytotoxic drugs during hyperthermia are shown in table II.

Case Reports

Gastrointestinal Tumours.—Six cases. One patient had an adenocarcinoma of the colon with large hepatic metastases enlarging the liver to 12 cm below the costal margin. After treatment the liver mass regressed to a lump 5 by 6 cm and the patient was alive and well at six months. The second patient, with a cholangio carcinoma of the liver, showed regression of hepatomegaly with complete clearance of jaundice (initial bilirubin 7·2 mg/100 ml) and resolution of gross ascites. The third patient had an undifferentiated carcinoma and was admitted to hospital as an emergency case with large-bowel obstruction. There was a mass 20 cm in diameter in his left iliac fossa and he had renal failure due to ureteric involvement. After treatment he had complete regression of the mass with a return of normal renal and bowel function. A fourth patient had some regression of hepatomegaly and the fifth showed necrosis on serial biopsy. There was symptomatic improvement in one patient with adenocarcinoma of the gall bladder.

Malignant Melanoma.—Three metastatic cases. Two patients showed regression of involved axillary nodes and the third showed regression of hepatomegaly though her secondary nodules did not change in size.

Breast Cancer.—Three cases. These patients had cancer en cuirasse and were in severe pain. In the first two there was relief of pain with discontinuance of opiates and regrowth of skin over the tumours. One of these patients died within 12 hours of a further treatment given for recurrence three months later. There appeared to be no pathological evidence of tumour necrosis and death was attributed to disseminated intravascular coagulation. The third patient died 48 hours after treatment with disseminated intravascular coagulation. In this case necropsy showed evidence of recent cell death in the tumour metastases, which involved liver, adrenal, both kidneys, skull, uterus, pancreas, vertebrae, and dura.

Miscellaneous.—One case of osteoblastoma was treated. Though the patient had pain relief there was no regression of the tumour.

TABLE II—*Results of Treatment with Hyperthermia in Combination with Chemotherapy*

Tumour Type	No. of Patients Treated	Previous Treatment			Objective Response	Subjective Response	No Response	Survival from Start of Thermotherapy (Weeks)
		Surgery	Radiotherapy	Chemotherapy				
Gastrointestinal tumours	6	4	1	1	5	5	0	32, 20, 20, 16, 12, 8
Carcinoma breast ..	3	3	3	2	2+1*	2	0	20, 12, 0·28
Melanoma	3	3	0	0	3	1	0	52, 44, 24
Osteoblastoma ..	1	1	0	0	0	1	0	12

* Necropsy evidence of recent tumour necrosis.

Complications

Complications may arise from the method, from the physiological response to high temperatures, or from the toxic effects of tumour breakdown. When one considers that these patients were maintained in an unconscious state at temperatures of over 41°C for a total of about 1,000 hours complications of a major character were remarkably few. The second patient treated, in 1966, before the present controlled method was evolved, developed ventricular fibrillation. This was due to her temperature reaching 43°C as a result of thermometer failure and was the only fatality directly attributable to induced hyperthermia.

Half of the patients developed a circumoral herpes simplex during the first session but not on subsequent treatments. Sore throats, pressure sores due to prolonged immobilization during treatments, and superficial burns in oedematous, hypoproteinaemic patients occurred.

Four adult patients died within 48 hours of hyperthermia; their deaths were associated with evidence of disseminated intravascular coagulation. In three necropsy showed recent tumour necrosis. Two children with an advanced form of neoplastic disease also died shortly after treatment. They were given opiates for relief of distress and died of respiratory complications. Another patient died of fibrosing alveolitis, possibly due to repeated exposure to the hot, moist, ventilating gases then in use (Henderson and Pettigrew, 1971) or as a result of treatment with bleomycin six months previously.

RECOVERY AFTER TREATMENT

Narcosis is maintained during treatment with short-acting barbiturates and the patient is awake before leaving the theatre. Patients with sensitive tumours show evidence of a systemic reaction after the first treatment, especially if it is prolonged. They develop a persistent tachycardia with a low blood pressure and may remain pyrexial for up to 48 hours. Recovery takes place more rapidly after a subsequent treatment if given within a week. After the first treatment patients may be managed on a day-stay basis, coming into hospital on the morning of treatment and being discharged the next day. Patients with unresponsive tumours show no toxic effects and are fully recovered within eight hours. If treatment is extended beyond four or five hours post-treatment jaundice may develop.

Discussion

There have been no deaths during hyperthermia in over 200 treatment sessions. Of the four adult deaths occurring within 48 hours of treatment all but one were associated with extensive tumour necrosis. In the series of patients treated there were no cures and few complete clinical remissions; however, the advanced nature of the disease in all the patients is emphasized. In general patients responding to treatment experienced a remarkable sense of well-being during the period of remission, with relief of tumour-evoked pain. The quality of life possible after even incomplete treatment of a responsive tumour has been our justification for treating such advanced cases. In doing this it has been established that the selective thermal killing of tumour cells can be extended to human tumours in vivo. Most patients treated with hyperthermia alone who showed initial tumour regression had recurrence of the tumour at about three months in a heat-resistant form.

Animal experiments indicate that at temperatures above 42°C normal cells start to undergo irreversible damage (Burger, 1970; Burger *et al.*, 1970). In this series it was found that at 42°C there was a rise in serum enzymes along with a post-treatment jaundice (Pettigrew *et al.*, 1974). This did not occur after treatment at 41·8°C, which was therefore taken as the maximum permissible therapeutic temperature. There are indications that a treatment period in excess of 20 hours would be needed at 41·8°C to produce total tumour necrosis (Johnson, 1940). This treatment period may become possible with a greater understanding of the physiological processes which occur at 41·8°C. Several workers have claimed that a synergism exists between hyperthermia and certain cytotoxic drugs (Stehlin, 1969; Giovanella *et al.*, 1970). By combining the two treatments it may be possible to produce total tumour necrosis in a shorter time. The rationale behind this, however, has recently been questioned (Palzer and Heidelberger, 1973 a). Though the numbers in this series were small it appeared that there was an enhanced effect when hyperthermia and chemotherapy were combined.

With any treatment regimen aiming at total tumour necrosis in one session the possibility of toxic products causing deleterious effects such as diffuse intravascular coagulation cannot be ignored (Leavy *et al.*, 1970; Peck and Reiquam, 1973). Yet with therapy given in multiple sessions other problems may be encountered. Work with transplanted animal tumours indicates that heating to a degree insufficient to produce a cure has a stimulatory effect on the spread and growth of metastases (Brett and Schloerb, 1962; Dickson and Ellis, 1974) and may allow repair of sublethal damage to the tumour cells to take place (Palzer and Heidelberger, 1973 b). Heat-resistant strains of cultured human tumours have been produced by exposure to sublethal hyperthermic damage (Selawry *et al.*, 1957). In this series some of the patients with responsive tumours who were treated with multiple sessions of heating without chemotherapy seemed to develop less sensitive tumours. Patients who responded to chemotherapy plus hyperthermia continued to respond to further combined treatments given when there was tumour recurrence.

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Requests for reprints should be sent to Mr. A. N. Smith, Department of Clinical Surgery, Western General Hospital, Edinburgh EH4 2XU.

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