ACTA RADIOLOGICA

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF DENMARK, FINLAND, NORWAY AND SWEDEN

Vol. 2 | New series | 1964
Fasc. 5 | THERAPY PHYSICS BIOLOGY | October

COMBINED THERAPY WITH 220 KV ROENTGEN AND 10 CM MICROWAVE HEATING IN RAT HEPATOMA

by

DONALD B. CATER, IAN A. SILVER and D. ANNE WATKINSON

A major problem in radiotherapy is cancer cells situated some distance away from their blood supply and therefore anoxic and radioresistant (THOMLINSON & GRAY 1955, GRAY 1961). Most recent attempts to solve this problem have been concerned with raising of the tumour oxygen tension by:

1. Inhalation of oxygen at atmospheric pressure (HULTBORN & FORSSBERG 1954, MITCHELL 1957 a, b, and 1960);
2. Subcutaneous injections of oxygen (VON SAAL & DALICHO 1957);
3. Inhalation of oxygen under increased pressure (CHURCHILL-DAVIDSON, SANGER & THOMLINSON 1955, 1957; EMERY, LUCAS & WILLIAMS 1960; SEAMAN, TAPLEY, SANGER et coll. 1961);
4. Intra-arterial infusion of hydrogen peroxide into the vascular supply of the tumour which will raise tumour oxygen tension to high levels (SILVER & CATER 1964).

All these methods have certain advantages and limitations (CATER & SILVER 1960, CATER, SCHOENIGER & WATKINSON 1963). Another possibility,

From the Departments of Radiotherapeutics (Director: Prof. J. S. Mitchell) and Veterinary Anatomy (Prof. J. D. Boyd) University of Cambridge, England. Submitted for publication 10 March 1964.

namely bringing both the normal tissues and the tumour to the anoxic level of radiosensitivity (WRIGHT & SHEWELL 1960) would not appear to be a practical therapeutic procedure at present, except possibly for limb tumours (CATER, HILL, LINDOP et coll. 1963). It was therefore decided to explore the possibilities of using a quite different technique for dealing with the anoxic, radioresistant cancer cell. When heat is developed in tissues by radiofrequency diathermy heating, the blood vessels will act as cooling pipes so that cells distant from the vessels should be preferentially heated. Thus it might be feasible to kill anoxic cancer cells by heat and the well oxygenated cells near the vessels by radiation (CATER, SILVER & WATKINSON 1962). We therefore decided to set up experiments to test the therapeutic effect of 10 cm microwave heating combined with roentgen therapy. Two factors greatly facilitate our project. Firstly, Dr Audrey Smith and Mr. W. J. Perkins of the Medical Research Council Laboratories, Mill Hill, very kindly loaned us a suitable 500 watt 'Magnetron 10 cm Microwave diathermy apparatus' (PERKINS 1955). Secondly, the paper by CRILE (1961) gave valuable data on the thermal death point of tumours in mice. The literature is reviewed in the discussion.

Materials and Methods

Male rats of the August strain were injected in the left thigh with transplantable hepatoma 223; after 5 days they were randomly allocated into 4 groups. Those in group A were given sham treatment, in group B they were irradiated, usually on the 7th day, in group C they were treated with microwave diathermy only, and in group D they were irradiated first and then treated with diathermy.

The rats to be irradiated were wrapped in lead with the left thigh protruding through a hole in the lead. A 220 kV 'Maximar' was used for the irradiation, with a 5 cm circle applicator to the dorsal aspect of the thigh and leg, FSD 41.5 cm and 1 mm Al as filter. The dose rate was 164 r/min with back scatter.

In the first experiment, the dose was 1 310 r, in experiments 2 to 4 the dose was 1 965 r, and in experiments 5 to 14, it was 2 620 r. All unirradiated rats were wrapped in lead for the appropriate time to simulate a mock irradiation.

The radiofrequency microwave heating was performed: a few hours after irradiation in experiments 1, 3, 4, 5, two days after irradiation in experiments 2, 10, 11, 12, and 14, three days in experiments 6, 7, 8, and four days in experiments 9 and 13. The apparatus used was made and described by PERKINS (1955). It had a magnetron of the continuous wave type with a power output of 500 W, operating at a frequency of 3 000 Mc/s, and a wave guide 7×3.5 cm in cross section. Preliminary experiments with water phantoms indicated that it would have to be operated at much below its maximum power output. The rats were anaesthetised with sodium amytal 70 mg/kg intraperitoneally (groups A and B were also anaesthetised). The tumour-bearing thigh was suspended in the microwave beam by a stocking of adhesive plaster. The body of the rat was well clear of the beam. In experiments 1 to 3, the temperature was estimated by time and the magnetron current and was checked by a thermocouple inserted immediately after the current was switched off. This was unsatisfactory because the temperature of the heated tumour varied from rat to rat. Then some very thin thermocouples were made by passing an insulated constantan wire down the lumen of a stainless steel dental needle, 0.5 mm in diameter, and soldering the end of the constantan wire into the pointed tip of the needle. When such a thermocouple was inserted into water-filled phantoms, parallel with the mouth of the wave guide and parallel with the wide axis of the mouth of the wave guide, there was no evidence that it picked up any power out of the beam at the levels of output which we were using. It was then possible to monitor continuously the temperature of the tumour during the heating (see Figs 2 and 3). In experiment 4, the tumour temperature was raised to 45° C for 5 min, with the beam directed at the lateral surface of the thigh; the rat was then turned round as quickly as possible and the tumour temperature was held at 45° C for 5 min, with the beam directed at the medial surface. In experiments 5 to 9, a temperature of 47° C for 5 min to each side of the limb was used. In experiments 12 and 13, 47° C for 8 min to the lateral aspect, and in experiments 10, 11 and 14, 47° C for 10 min to the lateral aspect of the limb. After experiment 5, it became obvious that all unirradiated rats (groups A and C) succumbed rapidly to the primary tumour, so in experiments 6 to 14 only groups B and D were used.

The after-care of the rats consisted of measuring the tumour with calipers for length, breadth and thickness. Any ulcerated areas were painted with 'Tinct. Benzoin Co' of the British Pharmacopoeia to prevent the rats eating the limb.

Results

The final technique developed during the series of experiments was designed to achieve the maximum cure rate. However, to obtain a sufficient number of results for analysis, all the experiments were grouped together. The tumour was very lethal and killed 100 per cent of group A (untreated controls) and group C (treated with microwave heating alone). The irradiated rats of group B survive longer but all died of primary and secondary tumours. The irradiated rats treated with diathermy (group D) survived for a signif-

Table

Number of rats with extensive metastases in aortic lymph nodes

	Group B (70 rats) Irradiation only	Group D (68 rats) Irradiation and microwave heating
Death due to primary tumour	27	16
Metastases large but primary tumour also a cause of death	16	17
Metastases large and caused death — Primary tumour small but viable tumour present	23	24
Metastases large and caused death — No primary tumour present	4	5
Long-standing cures or remissions	0	6 (449[1], 137[1], 293, 341[1], 219,[1] and 408[1] days, respectively)

[1] Indicates death due to recurrence at primary site after a long period of apparent cure.

icantly longer period of time. The details of the survival times are given below:

Sham-treated controls (group A)	21.62 ± 0.875	(n = 34)
Microwave heating only (group C)	21.54 ± 1.15	(n = 33)
Irradiated only (group B)	38.27 ± 1.17	(n = 70)
Irradiated plus microwave heating (group D)	59.37 ± 8.5	(n = 68)

The increase in mean survival of group D compared with that of group B is largely due to 6 long term survivors. All the rats in group B were dead by 68 days after inoculation of the tumour. In group D, 6 rats survived for 137 days or longer (see Table 1 for details). Using the method of FISHER (1948) the exact probability of this occurring by chance is 1.3 %.

Hepatoma 223 transplanted into the leg muscles of these August strain rats proved extremely difficult to cure. All the unirradiated rats of groups A and C died rapidly of the primary tumour, but many of the irradiated rats in groups B and D died partly or entirely due to large metastases in the aortic lymph nodes, as shown in the Table.

The size of the tumours in the thigh could be measured fairly accurately with calipers in three directions, length, breadth and thickness. This was done at suitable intervals in all the experiments. A rough estimate of the volume of the tumour was made by multiplying the length, breadth and thickness of the tumour together and dividing by 2.

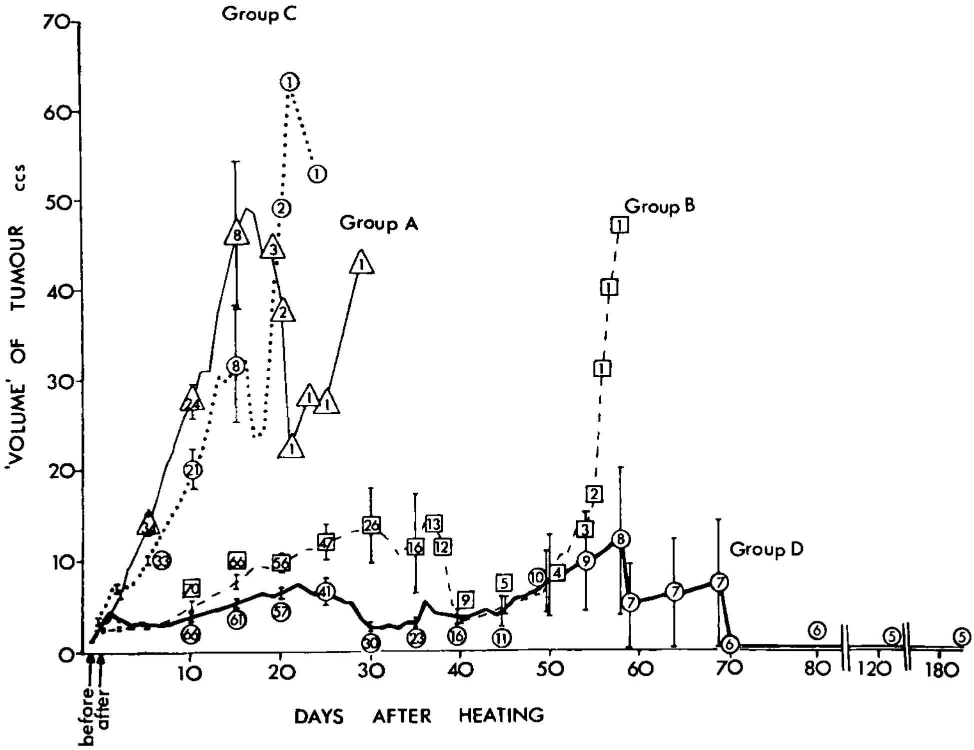

Fig. 1. 'Volume' of tumour = length × breadth × thickness/2 plotted against number of days after heating.
Group A △———△ controls (sham treatments)
Group B □— — —□ roentgen ray only
Group C ○· · · · ·○ microwave heating only
Group D ○———○ roentgen ray and then microwave heating. The number enclosed indicates the number of rats of that group surviving on that day. The standard errors of the means calculated at 5 day intervals are indicated ı—○—ı. For two days after microwave heating the tumours of group D are larger than those of group B, from 15 to 35 days they are significantly smaller. At 57 days, all of group B have died but there are 6 long term survivors in group D. Group C does not differ significantly from the controls group A. The time base is interrupted at 85 and 125 days.

The data on tumour size are given in Fig. 1. The mean tumour volume calculated from all the rats has been plotted against time after microwave heating, and the standard errors of the means are shown for every 5th day. The numbers in the circles record the number of rats surviving, so that a fairly complete picture of the result of the experiments can be built up from this figure. It will be seen that the microwave heating alone had little effect upon the rate of growth of the tumour compared with the sham-treated controls, or upon the survival of the rats. The rate of growth of the tumour was

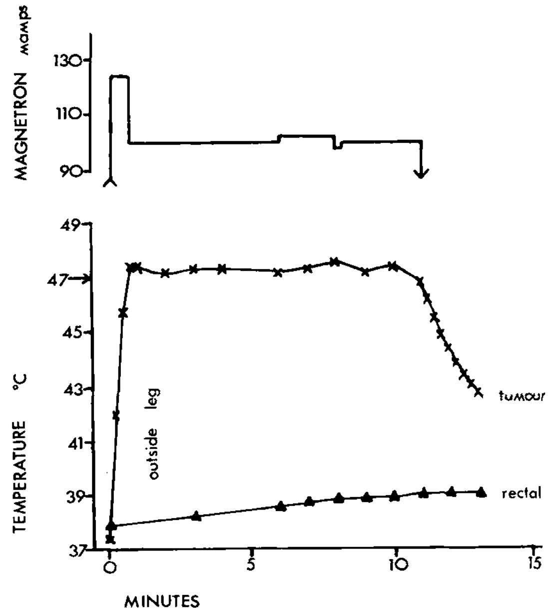

Fig. 2. The thermocouple inserted in the tumour shows that satisfactory control of tumour heating was achieved in this rat. The upper trace is the magneton current in mA, middle trace is tumour temperature, and the lowest trace shows the rise of rectal temperature of the rat.

much less in the irradiated rats and their survival was significantly prolonged. The mean size of the tumours in the irradiated and microwave-treated rats was significantly less at 15, 20, 25 and 30 days than in the rats treated by irradiation alone and their survival was significantly longer. An interesting point in Fig. 1 is the increased size of the heated tumours for one or two days after the microwave treatment.

The technical control of the microwave heating was greatly improved by insertion of the thermocouple so that the temperature could be raised to the desired level and held there. An example of good control is shown in Fig. 2. The temperature was raised steadily to the desired level of 47° C and held there by only minor adjustments of the current flowing through the magnetron. The rapid fall of tumour temperature, when the microwave heating ceased, indicated that the tumour blood supply had not been interrupted. The rise of rectal temperature was an indication of the heat supplied to the leg and also that the blood supply to the tumour and limb was acting as a cooling agent.

Sometimes it was difficult to control the temperature of the tumour at the desired level; an example of bad technical control is shown in Fig. 3. This figure is from experiment 5, in which the limb was heated first from the lateral and then from the medial aspect; it may be seen that marked changes of

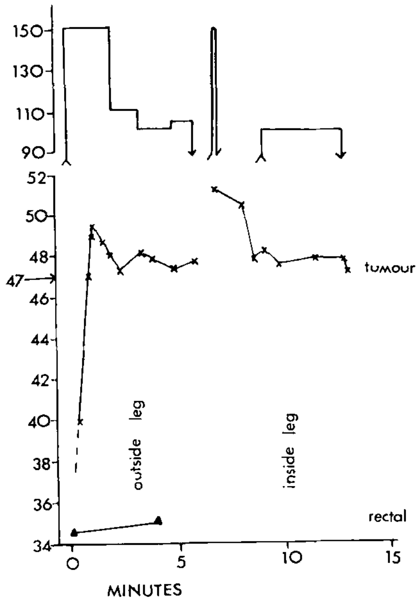

Fig. 3. Satisfactory control of tumour temperature was not achieved in this rat. Upper trace is the magnetron current in milliamps, middle trace is tumour temperature. In this rat the microwave was first applied to the dorsal aspect of the thigh. After 5 min at 47° C + the thermocouple was removed, the rat was turned round, the thermocouple was reinserted and the microwave was applied to the ventral aspect of the thigh.

magnetron current were needed because the temperature of the tumour overshot the desired level of 47° C. It is possible that this tumour had a poor blood supply or areas of degeneration. It was found that oedema of the foot or areas of thrombosis in the tumour or the overlying tissues were much more frequent when the temperature control was inadequate. In later experiments, in which the limb was heated only from the lateral surface, the temperature control was more precise and damage from overheating was much reduced. It is likely that heating only from the lateral side reduced the danger of thrombosis or spasm of the femoral vessels.

Discussion

Our findings on length of survival, rate of tumour growth, and number of long lasting cures or remissions, in August strain rats with hepatoma 223 transplanted into thigh muscles, all suggested that roentgen radiation plus microwave heating was a significantly better form of treatment than roentgen radiation alone. Better results might have been obtained if a higher dose of roentgen had been used, but 2 620 r was the highest dose that could be given as a single dose, and indeed it caused depilation and some desquamation of the skin. The results might have been better if we had used a more easily curable tumour without a high incidence of metastases. The microwave heating could not have been increased without danger of limb destruction. Ten minutes at 47° C was as near the limit as was safe to go. We used the roentgen radiation first, because (1) heating might render the tumour more hypoxic and thus reduce the effect of radiation, and (2) the microwave heating might tend to spread tumour cells and these would be less likely to cause metastases if they had been irradiated.

Our results are in line with those of a considerable number of workers who have recorded the beneficial effects of heating and radiation. Heat has been applied by a number of different methods, including fever, hot water, hot air, high frequency currents (conventional diathermy), radiofrequency heating of 6 to 12 metres wave length, radiofrequency in the microwave range (12.5 to 2 cm wavelength), electromagnetic heating with target particles in the tissue, and ultrasound used as heat.

WESTERMARK (1927) reviewed the prowess of the ancients with the red-hot iron, the pioneer work of F. WESTERMARK (1898) with hot water at 42 to 44° C, KEATING-HART (1909), using fulguration of superficial cancers with high-frequency currents, DOYEN (1910) with electrocoagulation by conventional diathermy, and MÜLLER (1910, 1912), who reported on 100 patients with advanced cancer treated by diathermy and roentgen ray therapy. WESTERMARK (1927) set out to answer the question: "Is it possible to affect a tumour in the tissues by heat alone in such a way that recession takes place without previous necrosis or removal?" He heated Flexner-Jobling rat carcinoma and Jensen sarcoma with high-frequency currents, measured tissue temperature with a thermocouple, and found that the tumour would disappear with 20 min at 48° C, 30 min at 47° C, 50 min at 46° C, 90 min at 45° C and 120 min at 44° C, in good agreement with the formula of Arrhenius for the rate of chemical reaction with temperature

$$K_{t_1} = K_{t_0} \cdot e^{\mu/2 \frac{T_1 - T_0}{T_1 \cdot T_0}} \text{; or } t_0 = t_1 e^{\mu/2 \frac{T_1 - T_0}{T_1 \cdot T_0}}$$

where μ is constant.

He found that at 48° C there was no appreciable difference between the time required to kill tumour and normal tissues, but at 44° C tumour was damaged more quickly by heat than normal tissues. He showed a differential effect of heat upon aerobic and anaerobic glycolysis of tumour compared with the effect of heat on Q_{O_2}, the glycolysis falling steadily with time to become zero at 90 min while Q_{O_2} remained constant until 60 min and then fell to zero by 90 min.

The literature has also been reviewed by TAYLOR (1936) and by SELAWRY, CARLSON & MOORE (1958). However, our primary purpose is to make an objective assessment of the usefulness, or otherwise, of heat as an adjunct to radiotherapy in the treatment of patients. It is therefore necessary to discuss separately the results which have been obtained with different methods of heating and, after taking into consideration the general dangers and pathological limitations which beset this form of treatment, to map out the possible lines along which useful progress might be made.

Artificial fever. Natural fever as in erysipelas or induced by Coley's fluid has been credited with producing spontaneous remissions of tumours. These rare remissions may have been due to the effect of temperature on the tumour cells, or to the destruction of tumour blood vessels by toxins active against endothelium, or to both. Artificial fever by hot air baths was used by WARREN (1935) on 32 hopeless tumour cases. Body temperatures of 41.5° C for 5 to 21 hrs were maintained, with or without palliative doses of roentgen rays. Shrinkage of tumour masses, and longer than expected survival, were reported. SCOTT (1944) also reported similar experiences with useful palliation but made no claims of cure. KLÄRNER & KLÄRNER (1958) reported that urethane-induced lung tumours in mice were significantly reduced in size by placing the mice in a thermostat at 36—38° C for 6 to 9 hrs daily.

2. *Local heating.* In vitro studies on the sensitivity of tumours to heat plus radiation were made by LEPPER (1914—15) and ROHDENBURG & PRIME (1921) who took fragments of Crocker sarcoma 180 and after heating them to 42°, 43° and 44° C for 30 min exposed them to various doses of roentgen rays and then injected them into mice as a test for tumour viability. They found a marked synergistic effect between heat and roentgen radiation.

In vivo investigations include those of ALLEN (1955), who subjected Crocker sarcoma 39, inoculated into the tails of rats, to oven-heat and roentgen radiation, and CRILE (1961) who immersed the legs of mice-bearing sarcoma 180 in a hot water bath. The time of heating required to destroy the tumour in more than 50 % of mice was 120 min at 42° C, 60 min at 43° C, 30 min at 44° C, 15 min at 45° C and at 46° C only 7.5 min. The normal tissues showed a similar exponential curve for heat damage but with a long time base (50 min at 46° C). CRILE's times for the heat destruction of tumours are thus shorter than WESTERMARK's. In fact, the latter writer's times for tumour correspond to CRILE's times for the destruction of normal tissues. CRILE (1961, 1962, 1963) found that heat and radiation are synergistic or at least additive in effect when given within a few hours of each other regardless of order. CRILE (1962) used a hot water bath at 44 to 46° C for 1 hr and then 600 r roentgen radiation for cutaneous metastases in a patient with breast cancer and in a case of osteogenic sarcoma.

3. *Conventional diathermy and roentgen or gamma radiation.* MÜLLER (1910, 1912) reported on 100 patients with advanced tumours of breast, bronchus, oesophagus, stomach etc, treated by diathermy and roentgen rays with complete retrogression in 32 % followed up for 2 years or less. There are numerous other reports in the literature but the conditions are too heterogeneous for useful correlation, and in many cases the follow-up times were far too short. CRILE (1962) reports treating metastatic carcinoma in the liver by insertion of a long surgical diathermy needle in order to produce slow heating followed immediately by 1 000 r roentgen radiation.

4. *Radiofrequency heating with wavelengths of 12 to 3 m.* This has been used in most of the investigations on the effect of heat plus roentgen rays. HILL (1934) quotes Dr Reiter who, in a preliminary communication to the 'Zürich International Conference on Radiology', claimed that 3.4 m ultra-short waves had the effect of destroying tumour cells. HILL treated a mouse tumour with a weak dose of 'ultra-short waves'. The animal was killed and the tumour cut into slices and half was exposed to 55 mg radium for 3 hrs. A normal tumour was treated in the same fashion and fragments of tumour treated in the 4 different ways were injected into mice. Only the tumour treated with the diathermy and the radium did not grow. FUCHS (1936, 1952) used 6 m radiofrequency heating for 10 to 20 min followed immediately by roentgen radiation. He ascribed the good clinical results to hyperaemia and acceleration of metabolism causing increased radiosensitivity. However, CATER & SILVER (1960) found no evidence to suggest that 12 m radiofrequency heating increased the oxygen tension of tumours. KORB (1939) had two patients each with 2 basal cell carcinomas. In each patient one tumour was treated by 1 m radiofrequency heating and roentgen rays and the other by roentgen rays only. In both cases the heated tumour was cured, the other persisted. BIRKNER & WACHSMANN (1949) measured the temperature of carcinomas of the skin with a benzol-in-quartz thermometer during 6 m radiofrequency heating. In the example quoted the temperature was 42° to 44° for 2.5 hours. In 82 patients radiofrequency heating alone produced regressions but no cures. Radiofrequency heating and roentgen radiation produced some cures, and repeated treatments gave good results, with the best results from radiofrequency heating plus a large dose of roentgen radiation.

5. *Radiofrequency heating, microwave (12.5 cm to 2 cm).* GESSLER, MCCARTY & PARKINSON (1950) were able to eradicate spontaneous mammary carcinoma in C3H mice by microwave heating alone. ALLEN (1955) cured Crocker sarcoma 39 in rats with 12.5 cm microwave heating for 10 to 20 min, to give

a temperature of 42° C, plus 1 500 to 2 000 r roentgen rays. CRILE (1962) used microwave heating and roentgen rays on spontaneous tumours in dogs and myoblastoma and osteogenic sarcoma in man.

6. *Heating by target particles in a high frequency magnetic field.* Radiofrequency waves subject the tissues to an alternating magnetic field which will produce eddy currents in conductors and vibrate magnetic particles. GILCHRIST, MEDAL, SHOREY, et coll. (1957) injected Fe_2O_3 of 20 to 100 mμ particulate size into lymph nodes and found that differential heating of the nodes due to magnetic hysteresis loss was marked at 1.2 megacycles and 255 oersteds. MEDAL, SHOREY, GILCHRIST, et coll. (1959), using 120 kcps and a magnetic field of 470 oersteds, found the tissue heating divided by 100 but the magnetic particle heating divided by 10. GILCHRIST (1960) in an editorial has discussed the possibilities of electromagnetic heating with target particles.

7. *Ultra-sound as heat.* HORVATH (1944) obtained surprisingly good results by the use of ultrasound on the superficial metastases of a reticulum-cell sarcoma in a patient. DITTMAR (1948) treated Walker carcinoma and Jensen sarcoma in rats, and ALLEN (1955) cured 2 rats with Crocker sarcoma 39 by ultrasound used as heat. WOEBER (1955) used combined roentgen rays and ultrasound for the treatment of dermatological conditions, and found that Walker carcinoma in rats could be cured by 350 r plus ultrasound while roentgen treatment alone required 600 r. NELSON, HERRICK & KRUSEN (1950a) reviewed the history and theory of ultrasound and its biological effects. They noted (1950, b) the preferential heating of bone and bone marrow by ultrasound. HERRICK (1953) also noted that the temperature of nerves rose to about twice that of the surrounding tissues, and heating to the critical range of 48.5° to 51.6° C caused nerve block. PAUL & IMIG (1955) measured the temperature and blood flow in dog and human muscle after heating with ultrasound. FRY, BARNARD, FRY & BRENNAN (1955) produced localised selective lesions in cat brain by crossing 4 focussed beams of ultrasound.

The *general inference* to be drawn from all these investigations is that heat given under the right conditions could be a useful adjunct to radiotherapy in the treatment of cancer. The possible dangers inherent in heat therapy must however be discussed. The selective heating of bone, bone marrow and nerve by ultrasound have just been mentioned, and MCAFEE (1962) describes the stimulatory effects of 12.2 cm microwaves on peripheral nerves when these reach a temperature of 45° to 47° C. SCHWAN & PIERSOL (1954, 1955) mention the dangers of cataract formation and preferential heating of hollow viscera, bone and metallic objects by microwaves, and ENGEL, HERRICK, WAKIM et coll. (1950) the effect of microwaves on bone marrow.

These particular dangers can be avoided by suitable technique but what is much more important is the strict limit which the pathological effects of toxic absorption set to tumour destruction. Thus there is a very definite limit to the amount of tumour tissue which it is safe to kill within a certain period of time. Tumours can be completely and rapidly destroyed by a number of different methods, the only trouble is that the toxic products from the dead tumour kill the patient. It cannot be reiterated too often that one of the most valuable properties of roentgen radiation is that it kills the tumour slowly, cell by cell, over a period of days or weeks, and so allows the host to deal with the inevitable toxic products from the breakdown of dead cells.

The limit which this elementary principle of pathology sets to the amount of tumour which can be safely killed per day would rule out at present the killing by heat (using conventional diathermy or short-wave radiofrequency heating) of large, deeply-seated tumours even if this could be done without damaging normal tissues. The heating of small, superficial tumours with surgical diathermy remains a practical proposition, especially with tumours of tongue and vulva which have recurred after radiotherapy. Microwave heating with thermocouple control could also probably be used for such tumours and could give greater depth of heat penetration. There is a possible field for heat treatment of sclerosing osteosarcomas in limbs by combined radiotherapy and diathermy or ultrasonic heating. The selective heating of bone might be used to advantage here. We hope to investigate the intra-arterial perfusion of heated saline in spontaneous osteosarcomas in dogs, as a possible line of attack on this radioresistant tumour. The techniques of GILCHRIST et coll. (1957), using electromagnetic heating of target particles, are promising but require considerable technical progress to make them applicable to patients.

We are left with the possibility of treating small portions of a tumour at a time with heat treatment sufficient to damage part or all of the cells in the treated area. Radiofrequency microwaves of wave lengths short enough to be directed in narrow beams so that two beams could be crossed are 100 % absorbed at a depth of 2 or 3 cm in tissue. There remains ultrasound which can be focussed and cross-beamed to heat small zones in tissue (FRY et coll. 1955), and with such an apparatus it should be possible to destroy daily a small portion of a deeply seated tumour by ultrasound used as heat.

CRILE (1963) draws attention to the fact that the tumour in vivo is much more susceptible to the destructive effects of heat than tumour cells in vitro. Thus tumours are transplantable shortly after exposure to heat but not if the tumour is left in situ for a few hours. CRILE suggests that this is due to the heat-induced inflammatory reaction impairing tumour bloodflow. He found that injections of 5-hydroxytryptamine (5-HT) 2.5 mg into the tumour immediately before heating greatly increased the susceptibility of the tumour to heat. The finding by CATER, GRIGSON & WATKINSON (1962) that 5-HT markedly lowers the oxygen tension in tumours and abolishes the response to oxygen inhalation even when the animal breathes oxygen at 5 atmospheres absolute (CATER, SCHOENIGER & WATKINSON 1963) probably means that 5-HT markedly slows the blood flow through tumour and therefore should increase the effect of heat on tumours. It might be possible to mimic the effect of heat on tumours with 5-HT or with some other agent to which tumour vessels are more responsive than normal vessels. This might be done with less danger and inconvenience than by techniques of tissue heating. Circulatory stasis might be more effective in destroying tumour cells than simple anoxia.

There still remains one other possibility. The early literature on diathermy heating contains more than one statement that tumours were sensitive to certain wave lengths but not to others. HILL (1934) quotes Dr Reiter who claimed that 3.4 m waves were effective. Wave lengths between about 10 m and 20 cm are not used for medical purposes because of 'Post Office Regulations', and little biological investigation has been done in this range. It is just possible that there might be a frequency to which DNA or the chromosomes would resonate, and application of such a frequency plus radiation might have very interesting possibilities. The frequencies used for television ought to be examined to exclude this possibility as an elementary safety precaution.

Acknowledgements

Financial help from the British Empire Cancer Campaign is gratefully acknowledged (authors D.B.C. and D.A.W. received full time support). Our warm thanks are due to Professor J. S. Mitchell for advice and encouragement, to Dr Audrey Smith and Mr W. J. Perkins of the National Institute for Medical Research, London, for the loan of the 'Magnetron Microwave Diathermy apparatus', to Professor Lamerton of the British Empire Cancer Campaign for gifts of August strain rats, and to Mr J. L. Haybittle of the Radiotherapeutic Centre, Addenbrooke's Hospital, for help with the statistical analyses.

SUMMARY

Combined therapy with 2 620 r of 220 kV roentgen rays and subsequent 10 cm microwave heating of tumour to 47° C for 8 to 10 min cured some rats with hepatoma 223 transplanted in the leg. In rats treated by radiation alone, or diathermy alone, there were no long-term survivors, the mean tumour size was greater, and the mean survival time was significantly shorter, than in rats treated by the combined therapy.

ZUSAMMENFASSUNG

Eine Kombinationstherapie mit Röntgenstrahlen von 2 620 r/220 kV und anschliessender, 8 bis 10 Minuten dauernder 10-cm-Mikrowellen-Erhitzung des Tumors auf 47° C heilte einige Ratten, denen Hepatoma 223 in das Bein verpflanzt worden war. Keine von den Ratten, die nur mit Bestrahlung oder mit Diathermie behandelt wurden, überlebte längere Zeit; die durchschnittliche Tumorgrösse war erheblicher und die durchschnittliche Überlebenszeit in signifikantem Masse geringer als bei Ratten, die der genannten Kombinationstherapie unterzogen worden waren.

RÉSUMÉ

Le traitement associé par 2 620 r de rayons roentgen sous 220 kV et par l'échauffement de la tumeur à 47° C pendant 8 à 10 minutes par les micro-ondes de 10 cm a guéri certains rats ayant un hépatome 223 greffé sur la patte. Chez les rats traités seulement par les radiations, ou seulement par les micro-ondes, il n'y a pas eu de survivants à long terme, le volume moyen des tumeurs était plus grand et la durée moyenne de survie était plus courte que chez les rats traités par le traitement associé.

REFERENCES

Allen F. M.: Biological modification of effects of roentgen rays. II. High temperature and related factors. Amer. J. Roentgenol. 73 (1955), 836.

Birkner R., and Wachsmann F.: Über die Kombination von Röntgenstrahlen und Kurzwellen. Strahlentherapie 79 (1949), 93.

Cater D. B., and Silver I. A.: Quantitative measurements of oxygen tension in normal tissues and in the tumours of patients before and after radiotherapy. Acta radiol. 53 (1960), 233.

— Grigson C. M. B., and Watkinson D. A.: Changes of oxygen tension in tumours induced by vasoconstrictor and vasodilator drugs. Acta radiol. 58 (1962), 401.

— Schoeniger E. L., and Watkinson D. A.: Effect of breathing high pressure oxygen upon tissue oxygen tension in rat and mouse tumours. Acta radiol. 1 (1963), 233.

— Silver I. A., and Watkinson D. A.: Combined X-ray and microwave therapy. A. R. Brit. Emp. Cancer Campgn 40 (1962), 375.

— Hill D. W., Lindop P. J., et coll:. Oxygen washout, studies in the anesthetized dog. J. appl. Physiol 18 (1963), 888.

Churchill-Davidson I., Sanger C., and Thomlinson R. H.: High-pressure oxygen and radiotherapy. Lancet 1955: I, p. 1091.

— — — Oxygenation in radiotherapy: clinical application. Brit. J. Radiol. 30 (1957), 406.

Crile Jr G.: Heat as an adjunct to the treatment of cancer. Cleveland Clin. Quart. 28 (1961), 75.

— Selective destruction of cancers after exposure to heat. Ann. Surg. 156 (1962), 404.

— The effects of heat and radiation on cancers implanted on the feet of mice. Cancer Res. 23 (1963), 372.

Dittmar C.: Über die Wirkung von Ultraschallwellen auf tierische Tumoren. Strahlentherapie 78 (1948), 217.

Doyen E.: Traitement local des cancers accesibles par l'action de la chaleur au dessus de 55°. Rev. Thérap. méd.-chir. 77 (1910), 551, 577.

EMERY E. W., LUCAS B. G. B., and WILLIAMS K. G.: Technique of irradiation of conscious patients under increased oxygen pressure. Lancet 1960: I, p. 248.

ENGEL J. P., HERRICK J. F., Wakim K. G., et coll.: Effect of microwaves on bone marrow and adjacent tissues. Arch. phys. Med. 31 (1950), 453.

FISHER R. A.: 'Statistical methods for research workers', p. 98. 10th edition. Oliver & Boyd, Edinburgh 1948.

FRY W. J., BARNARD J. W., FRY F. J., and BRENNAN M. S.: Ultrasonically produced localised selective lesions in the central nervous system. Amer. J. phys. Med. 34 (1955), 413.

FUCHS G.: Über die Sensibilisierung röntgenrefractärer Neoplasmen durch Kurzwellen. Strahlentherapie 55 (1936), 473.

— Zur Sensibilisierung maligner Tumoren durch Ultra-Kurzwellen. Strahlentherapie 88 (1952), 647.

GESSLER A. E., MCCARTY K. S., and PARKINSON M. C.: Eradication of spontaneous mouse tumours by high frequency radiation. Exp. Med. Surg. 8 (1950), 143.

GILCHRIST R. K.: Potential treatment of cancer by electromagnetic heating. Surg. Gynec. Obstet. 110 (1960), 499.

— MEDAL R., SHOREY W., et coll.: Selective heating of lymph nodes. Ann. Surg. 146 (1957), 596.

GRAY L. H.: Radiobiologic basis of oxygen as a modifying factor in radiation therapy. Amer. J. Roentgenol. 85 (1961), 803.

HERRICK J. F.: Temperatures produced in tissues by ultrasound: Experimental study using various technics. J. acoust. Soc. Amer. 25 (1953), 12.

HILL L.: Actions of ultra short waves on tumours. Brit. med. J. (1934, ii), 370.

HORVATH J.: Ultraschallwirkung beim menschlichen Sarkom. Strahlentherapie 75 (1944), 119, 126.

HULTBORN K. A., and FORSSBERG A.: Irradiation of skin tumours during pure oxygen inhalation. Acta radiol. 42 (1954), 475.

KEATING-HART W.: La fulguration et ses résultats dans le traitement du cancer d'après une statistique personnelle de 247 cas. Maloine, Paris (1909).

KLÄRNER P., and KLÄRNER R.: Effect of heat, alloxan diabetes, thyroxin and other agents on induced lung tumours. Z. Krebsforsch. 62 (1958), 297.

KORB H.: Erhöhung der Wirkung von Röntgenstrahlen durch lokale Kurzwellenhyperthermie. Strahlentherapie 65 (1939), 649.

LEPPER E. H.: Experiments to determine whether variations in temperature influence effects produced when malignant cells are irradiated by radium bromide. Arch. Middx. Hosp. 33 (1914—15), 77.

MCAFEE R. D.: Physiological effects of thermode and microwave stimulation of peripheral nerves. Amer. J. Physiol. 203 (1962), 374.

MEDAL R., SHOREY W., GILCHRIST R. K., et coll.: Controlled radio-frequency generator for production of localized heat in intact animal. A.M.A. Archiv. Surg. 79 (1959), 427.

MITCHELL J. S. (a): Clinical trials of radiosensitizers. Combination of oxygen inhaled at athmospheric pressure, Synkavit and X-ray therapy. Animal experiments. A. R. Brit. Emp. Cancer Campgn 35 (1957), 267, 269, 270.

— (b) Some clinical and laboratory studies of chemical radiosensitizers. Acta Un. int. Cancr. 13 (1957), 450.

— Some clinical and laboratory studies of chemical radiosensitizers, including the design and conduct of clinical trials. *In:* Studies in radiotherapeutics, pp. 80—165. Blackwells, Oxford 1960.

MÜLLER C.: Eine neue Behandlungsmethode bösartiger Geschwülste. Münch. med. Wschr. 57 (1910), 1490.
— Therapeutische Erfahrungen an 100 Kombinationen von Röntgen und Hochfrequenz resp. Diathermiebehandlungen bösartiger Neubildungen. Münch. med. Wschr. 59 (1912), 1546.
NELSON P. A., HERRICK J. F., and KRUSEN F. H. (a): Ultrasonics in medicine. Arch. phys. Med. 31 (1950), 6.
— — — (b) Temperatures produced in bone marrow, bone and adjacent tissues by ultrasonic diathermy. Arch. phys. Med. 31 (1950), 687.
PAUL W. D., and IMIG C. J.: Temperature and blood flow studies after ultrasonic irradiation. Amer. J. phys. Med. 34 (1955), 370.
PERKINS W. J.: A magnetron microwave diathermy apparatus for reaminating rats from 0° C. Electronic Engng 27 (1955), 394.
ROHDENBURG G. L., and PRIME F.: Effect of combined radiation and heat on neoplasms. Arch. Surg. 2 (1921), 116.
VON SAAL H., und DALICHO W. A.: Frühergebnisse der Röntgentherapie von Hauttumoren bei lokaler Sauerstoffzufuhr. Strahlentherapie 102 (1957), 31.
SEAMAN W. B., TAPLEY N. DU V., SANGER C., et coll.: Combined high-pressure oxygen and radiation therapy in the treatment of human cancer. Amer. J. Roentgenol. 85 (1961), 816.
SCHWAN H. P., and PIERSOL G. M.: The absorption of electromagnetic energy in body tissues; review and critical analysis. Amer. J. phys. Med. 33 (1954), 371.
— — Absorption of electromagnetic energy in body tissues; review and critical analysis; physiological and clinical aspects. Amer. J. phys. Med. 34 (1955), 425.
SCOTT L. D.: Summary of results of combined fever and X-ray therapy in treatment of hopeless malignancies. J. nat. med. Ass. Tuskegee Ala. 36 (1944), 184.
SELAWRY O. S., CARLSON J. C., and MOORE G. E.: Tumor response to ionizing rays at elevated temperatures; a review and discussion. Amer. J. Roentgenol. 80 (1958), 833.
SILVER I. A., and Cater D. B.: Radiotherapy (and chemotherapy) for domestic animals. II. The treatment of malignant tumours in dogs and cats. To be published in Acta radiol. Therapy Physics Biology.
TAYLOR H. J.: Effect of ultra high frequency currents combined with non-lethal doses of radium radiations upon experimental rat tumours. Brit. J. Radiol. 9 (1936), 467.
THOMLINSON R. H., and GRAY L. H.: Histological structure of some human lung cancers and possible implications for radiotherapy. Brit. J. Cancer 9 (1955), 539.
WARREN S. L.: Preliminary study of effect of artificial fever upon hopeless tumor cases. Amer. J. Roentgenol. 33 (1935), 75.
WESTERMARK F.: Über die Behandlung des ulcerierenden Cervixcarcinoms mittels konstanter Wärme. Zbl. Gynäk 22 (1898), 1335.
WESTERMARK N.: The effect of heat upon rat-tumors. Skandinav. Arch. Physiol. 52 (1927), 257.
WOEBER K.: Combined X-ray and ultrasound treatment for dermatological conditions; biological foundations and clinical applications. Amer. J. phys. Med. 34 (1955), 376.
WRIGHT E. A., and SHEWELL J.: Long term effects of irradiation in animals protected by anoxia. High-dose experimental radiotherapy during anoxia. A. R. Brit. Emp. Cancer Campgn 38 (1960), 306, 307.