

**WHOLE BODY HYPERTHERMIA**

The development of and experience with a clinical method

**TOTALE LICHAAMSHYPERThERMIE**

De ontwikkeling van en ervaring met een klinische methode

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# INTRODUCTIONARY

Section I





# INTRODUCTION

## Chapter I

### History

The concept that hyperthermia may be useful as a modality for the treatment of malignant tumours is not as recent as it may seem. The history of the use of increased temperature for tumour treatment has been described by a number of authors and one of these reviews dates from 1927! (Westermarck, 1927) As long ago as around 2000 years BC, Ramajana used ferrum candens to extirpate tumours. Cauterisation of small and non-ulcerating tumours was also recommended by Hippocrates (460-377 BC). In the 15th century, Leonides employed heat for the treatment of large ulcerating tumours, particularly for tumours of the breast. Ferrum candens was used both for destruction of the tumour and to control the bleeding. Ferrum candens was only infrequently used after this period as increasing skill in controlling haemorrhaging by blood vessel ligation resulted in growing use of the scalpel. However, the high temperature used in the above mentioned techniques, is quite different from the temperature range used nowadays in the treatment of cancer.

The concept that tumour tissue can be destroyed by a temperature increase of only a few degrees above the normal physiological level also has a long history. Kluger (1980) describes how, in the 4th century AC, Rufus of Ephesus

had observed the beneficial role of fever, and had advocated the use of fever induction for the treatment of, among other diseases, malignant tumours. In the 19th century, two publications appeared reporting tumour regression and even cure of patients following infection accompanied with high fever (Busch 1866, Bruns 1888). At the end of the 19th century, Coley was administering bacterial pyrogens to induce pyrexia in cancer patients. In a review, his daughter (Nauts, 1982B) states that complete regression and five-year survival had occurred in 46% of 523 inoperable cases and in 51% of 374 operable cases. The beneficial effects of such fever therapy are attributed, according to some immunotherapists (Mastrangelo et al, 1984), to stimulation of the immunological system. The observation that results improved when higher temperatures were attained (Nauts, 1982B), however, can be interpreted by the finding that heat itself is a cytotoxic agent. In the last decade of the 19th century, several observations were made that are relevant to the present-day status of

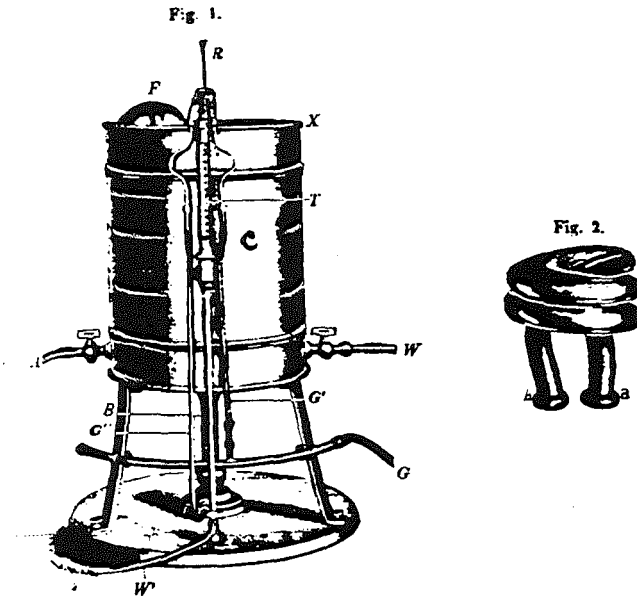


Fig. I - 1 HYPERTHERMIA A NEW CANCER TREATMENT MODALITY ?

The system used by Westermark (1898!) to heat malignant tumours of the uterine cervix. Water heated in the cylinder ("fig. 1") flows through the coil ("fig. 2") which is placed against the cervical tumour. Westermark observed good palliative results when tumour temperatures of 42-44°C were achieved.

hyperthermia.

In 1898 Westermark (Westermark, 1898) described the results following treatment of uterine tumours, using hot water circulating within a metal tube placed around the cervix (figure I-1). He reported that by using temperatures of at least  $42^{\circ}\text{C}$  within the tube, the symptoms of large ulcerating and bleeding tumours could be alleviated. He also found that, when higher temperatures were employed, the time necessary for symptom release became shorter.

In the period 1900-1966, publications on hyperthermia began to appear somewhat more frequently. These reports include investigations on the effect of hyperthermia in experimental tumour systems, both in vivo and in vitro, fever therapy, high frequency induction of hyperthermia, comparisons of normal and tumour cell sensitivity, the time-temperature relationship with regard to hyperthermia effect, the combination of hyperthermia and radiotherapy, and many more topics that are even now still being investigated.

The relatively low level of interest in hyperthermia before 1967 was probably due to the rapid developments in cancer treatment modalities such as surgery, radiotherapy and chemotherapy. Moreover, any existing interest was hindered by the many technical difficulties involved in the application of hyperthermia.

The present revival of research into hyperthermia is believed to start with Cavaliere's publication in 1967, in which he describes how animal tumour cells are damaged by heat to a greater extent than normal cells, and how hyperthermic regional perfusion in limbs of patients ( $41.5^{\circ}\text{C}$  -  $43.5^{\circ}\text{C}$ ) resulted in complete disappearance of tumour in 10 of 22 patients (Cavaliere et al, 1967). Since 1967, the increase in interest in hyperthermia, as measured by the number of publications and the number of participants in (international) meetings, seems to follow an exponential curve. A large number of investigations was performed on the effect of hyperthermia in experimental tumour systems, on cellular as well as tissular level. The aims of these studies were, and still are, to learn how hyperthermia acts and, finally, how hyperthermia can be applied optimally to patients. The outcome of these investigations has been promising from the start: hyperthermia results in cell death and, thanks to physiological differences between tumour tissue and normal tissue, results specifically in tumour cell death up to a certain dose level. Furthermore, hyperthermia effect appeared to be complementary to radiotherapy effect in tumour tissue, thus providing a desirable addition to local tumour treatment (see chapter II). These promising results of experimental research were, almost immediately, followed by an increasing number of clinical investigations.

Participation in the hyperthermia research at the Rotterdam Radio-Therapeutic Institute originates from 1976, when we received, by courtesy from Messrs Siemens, a "hyperthermia cabin", an apparatus with which hot air, radio-frequency and microwave energy could be simultaneously used to induce increased temperatures in tumours in patients.

### Objectives

The ultimate aim of the Rotterdam investigation was the hyperthermic treatment of human tumours, in order to eliminate those cell populations which are resistant to other treatment modalities. By the time that this investigation was started, only few publications on the clinical application of local hyperthermia had appeared (Holt 1975, LeVeen et al 1976, Hornback et al 1977). In these publications information on tumour temperatures achieved generally was missing. One of the problems anticipated to occur during local hyperthermia was the influence of blood flow on temperature distribution. The cells around a blood vessel entering the tumour, which transports blood at core temperature, will not be heated much above that core temperature which is about 37°C under physiologic circumstances (Cater et al 1964). In order to ensure a temperature increase up to higher levels for all tumour cells, the blood entering the tumour has to be prewarmed. This was the reason that a study was designed to develop a technique for, and investigate the benefits of, the clinical application of whole body hyperthermia (WBHT) in combination with additional local tumour heating. Even with this combination, the tumour cells in well oxygenated areas probably will survive a hyperthermia dose of 2 hours at 41.8 - 42°C, which may be the lowest dose achieved within the tumour. Therefore the need for simultaneous administration of other cell killing agents (radiotherapy, chemotherapy) was anticipated.

The questions to be answered by our investigation were concerned with various topics. In the first place, it had to be established how the equipment available could be used optimally in order to obtain WBHT as rapid, homogeneous and safe as possible, and if the technique would be comparable to other techniques used for induction of WBHT. The first step in this feasibility study was done by performing animal experiments, which are described in chapter IV. On the basis of the outcome of these animal experiments it was decided which technique would be used in the clinical study. Initial experience in thermometry during WBHT in humans was obtained by participation in hyperthermic treatment of 3 patients in two other clinics. This feasibility study was continued during the clinical study until patient no. 10; the treatment technique was

improved gradually on the basis of experience obtained.

For the clinical study (described in chapter V, VI and VII), patients were selected for whom the available -conventional- therapy was judged insufficient to achieve good results, whether palliative or curative.

The objective of the clinical study covered also the question of patient's tolerance: would the patients tolerate the treatment, whether WBHT alone or in combination with radiotherapy or chemotherapy, and would it be possible to conclude on any further selection parameters than those known from previous publications on WBHT. The clinical study further included questions about positive effects of the treatment such as objective tumour response and pain relief. As patients with various kinds of tumours were admitted to the study, differences in sensitivity to hyperthermia between the various tumours as confirmed by histology might become apparent. The ultimate question of this study was whether WBHT treatment would result in a profit to the individual patients or not, which could be estimated by weighing the costs against the profits. The question about the future of WBHT as induced by our "adapted Pompe Siemens cabin method", finally, could be answered by the evaluation of the overall results in the whole group of patients.

Before the description of our study is started, some introductory information is given. In chapter II, some relevant aspects of thermobiology are presented to give a background of knowledge about cellular and tissue reactions to hyperthermia. In chapter III, the potential techniques for the induction of hyperthermia are described, including information on thermophysiology, thermometry and a review of WBHT investigations performed by others.



# THERMOBIOLOGY

## Chapter II

### Thermobiology

An increase in the temperature of biological materials of only a few degrees above normothermia already causes damage to the cells and even cell death. Several reviews on this subject have appeared in the last years (Field and Bleeheh 1979, Dewey et al. 1980, Stewart and Gibbs 1984). The degree of damage depends on many factors. Firstly, the "dose" of hyperthermia administered to cells is of great importance. Hyperthermia dosage can be described as a function of the temperature and the exposure time. Westermarck (1898) has already described how treatment duration can be shortened when higher temperatures are applied. Westermarck junior (1927) presented the relationship between time and temperature for destruction of rat tumours, and introduced the use of a formula derived from the Arrhenius equation in his description of a hyperthermia dose-effect relationship. The time-temperature relationship for iso-effect can be mathematically described as

$$t_0 = t_1 R^{(T_0 - T_1)}$$

(in which  $t_0$  = time at reference temperature;  $t_1$  = time at temperature measured;  $T_0$  = reference temperature;  $T_1$  = temperature measured and R being a constant) (Sapareto 1982).

The above formula has been shown to be applicable for the damaging effect found for both tumour and normal tissues in experimental systems, *in vitro* and *in vivo*. A review by Field and Morris (1983) on time-temperature relationships has recently appeared. The findings are in general that with an increase of temperature of  $1^{\circ}\text{C}$  within a certain range, the treatment duration can be halved to obtain the same effect. Most investigators have found in addition that at moderate to low temperatures, below  $42$  to  $43^{\circ}\text{C}$ , this relationship changes such that a  $1^{\circ}\text{C}$  decrease in temperature must, in order to obtain the same level of effect, be compensated by an increase in treatment duration of a factor ranging from 2.7 to 33, with a mean value of 6. These findings are partly based on clonogenic cell survival studies, of which the results can be presented by cell survival curves. An example of cell survival curves is given in figure II-1. On the abscissa the dose is given and on the ordinate the sur-

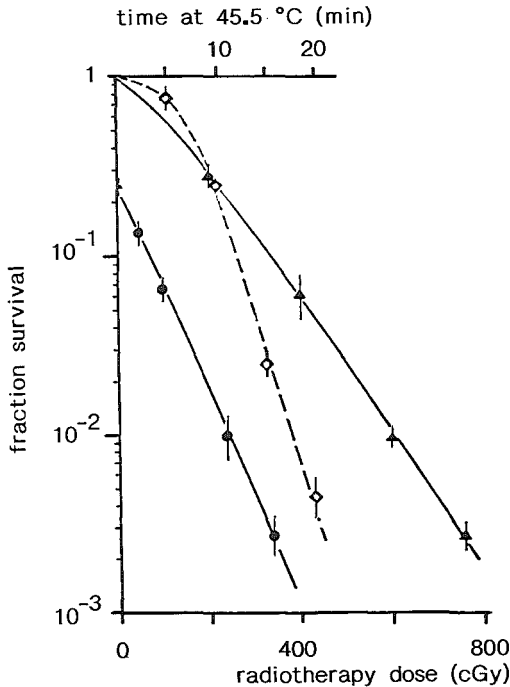


Fig. II - 1 CLONOGENIC CELL SURVIVAL AFTER HEAT AND RADIATION

Survival of  $T_1$ -cells (a human kidney cell line) following radiotherapy ( $\blacktriangle$ ), hyperthermia ( $\diamond$ ) and a combination of both treatment modalities (10 minutes hyperthermia and radiotherapy;  $\bullet$ ). Hyperthermia dose is given as minutes at  $45.5^{\circ}\text{C}$ . This figure shows how the "shoulder" of the survival curve of the radiation-alone treatment disappears and the survival curve becomes steeper when hyperthermia is given additionally.

Data from Westra, 1971.



living fraction of cells, on a logarithmic scale. A cell survival curve following radiotherapy is generally characterized by a "shoulder" and a part which is straight on the semilogarithmic scale, the exponential part. The shoulder is characterized by a value for  $D_q$ : the point of intersection of the straight part with the level of 100% survival (in dose). The exponential part can be described by its slope which is given as  $D_0$ : the increment of dose necessary to reduce the surviving fraction to 37%. The use of these mathematics renders the comparison between various survival curves possible.

Secondly, there is a great variation between different cell types in their sensitivity to heat, some cells being a factor of 10 or more higher in sensitivity than others, expressed as the  $D_0$  value of the exposure time (Raaphorst et al. 1979). The stage of the cell in the mitotic cycle also influences cell sensitivity to heat. In contrast with cell sensitivity to X-rays, cells in S-phase (synthesising DNA) appear the most sensitive to heat (Westra and Dewey, 1971).

Thirdly, it has been demonstrated that environmental factors are of major importance in cellular response to heat treatment. Hypoxic cells and cells in an acidic or nutrient-deficient environment are more sensitive to hyperthermia. (Overgaard and Nielsen 1980, Hahn 1982, Wike-Hooley et al. 1984B).

Fourthly, the degree of thermal damage is influenced by previous heat treatment. It has been demonstrated that thermotolerance, a term used to describe the relative resistance to hyperthermia, is induced when cells are either heated continuously for more than 3 hours at temperatures of 40-42.5°C, or receive a second heat treatment following a primary dose. Thermotolerance develops rapidly after a first heat treatment, reaching a maximum within 24 hours. Thereafter thermotolerance decays slowly over a period varying from 3 to over 14 days. The decay of thermotolerance was observed to be slower in normal tissue than in tumour tissue, which again may result in a selective effect of heat on tumour tissue (Urano and Kahn 1986) when hyperthermia is given fractionated. Thermotolerance also arises when step-up heating is performed, i.e. heating at a relatively low temperature prior to heating at a higher temperature. (Henle and Dethlefsen 1978, Urano 1986, Hahn and Shiu 1983B).

On the contrary, thermal sensitivity can be increased by using step-down heating, i.e. heating for a short time at a high temperature prior to heating at a lower temperature. (Nielsen et al. 1982, Urano and Kahn 1983).

Mechanisms which were observed to be involved in the effect of hyperthermia are listed in table II-1.

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Table II-1 OBSERVED MECHANISMS OF HYPERTHERMIA EFFECT

- Injury to cell membrane
  - Inhibition of respiration
  - Inhibition of ribosomal RNA synthesis
  - Denaturation to chromosomal proteins
  - Inhibition of DNA synthesis
  - Inhibition of protein synthesis
  - Release of hydrolytic enzymes from the lysosomes
  - Induction of vascular stasis
- 

From reviews by Dewey et al. (1977), Reinhold and Endrich (1986), and Streffer (1985).

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Some investigations have suggested that neoplastic cells may be intrinsically more sensitive to heat than normal cells (Giovannella et al. 1976, Flentje et al. 1984), but this apparent difference has not been confirmed in more detailed studies (Dewey et al. 1977). Anyhow, as conditions such as hypoxia, low environmental pH and nutrient deficiency are likely to occur in tumours (see next paragraph) due to the relative insufficiency of tumour circulation, these factors are more important for the effects of hyperthermia acting as a tumour specific treatment modality.

#### Tumour physiology under normothermic conditions

Tumours are composed of tumour cells and supporting tissues. Generally, the supporting tissues originate from the normal host tissues. Tumour cells proliferate intensively and easily overgrow their vascular system (Shubik 1982). Endrich et al. (1982) describe how, in an experimental melanoma, the capillary density per unit of tissue decreases with increasing tumour sizes. Interstitial edema, caused by filtration of fluid into the extravascular space, combined with an increase in number of tumour cells by proliferation, compress a great number of nutrition capillaries. The result is a self-destruction of tumour due to deficiency of oxygen and nutrients. This process is less outspoken at the margins of the tumour, where proliferation with

accompanying infiltration occurs without causing compression.

Therefore, tumour blood flow is heterogeneous, in general the peripheral regions of tumours are well perfused whereas in the inner regions poorly perfused areas exist (Tannock 1972). This was experimentally demonstrated, e.g., by Endrich (1979). Overall tumour blood flow is often lower than the blood flow of normal tissue. This has also been demonstrated for human tumours, using the  $^{133}\text{Xe}$  clearance technique (Mäntylä 1979).

The relative insufficiency of perfusion in tumours has the consequence that, in parts of the tumour, tumour cells have a deficient oxygen and nutrient supply. It was shown that the oxygen diffusion distance from a supporting capillary varied from 50-230  $\mu\text{m}$  (Thomlinson and Gray 1955, Boag 1969, Tannock 1972). Past this distance, cells become hypoxic and nutrient-deprived. This can further result in necrosis.

Hypoxia necessitates anaerobic glycolysis for the production of energy, resulting in the forming of lactic acid and other metabolites. As lactic acid is inefficiently removed, the interstitial pH decreases. Tumour pH has been demonstrated to be lower than normal tissue pH in many experimental tumour systems and also in human tumours (Van den Berg et al. 1982, Wike-Hooley et al. 1985). This heterogeneous composition of tumours has further been confirmed by observations following treatment by hyperthermia alone of experimental and human tumours. In the experimental sandwich-tumour-system, Reinhold et al. (1978) observed the central parts of the tumour to become necrotic following hyperthermia treatment of 1 hr at  $42.5^{\circ}\text{C}$ . In human tumours, regression has been observed following hyperthermic treatment at various levels, either whole body (Van der Zee et al. 1983), local or regional perfusion hyperthermia (Van der Zee unpublished data), followed by regrowth from the tumour margins after a period of about 3 weeks. These findings may demonstrate the specific heat sensitivity of the probably hypoxic cells in the centre of tumours.

Moreover, the lower bloodflow in tumours in comparison to that of normal tissues, will result in higher temperature increase in tumour tissue when a local heating technique is externally applied, as the cooling which depends mainly on tissue blood flow will be less in tumour tissue than in normal tissue. This higher temperature results, during local hyperthermia, once more in a specific tumour cell killing effect.

#### Hyperthermia effects on tumour physiology

The physiological reaction of normal living tissues to a rise in temperature is a change in blood flow, the amount of which depends on the level of tem-

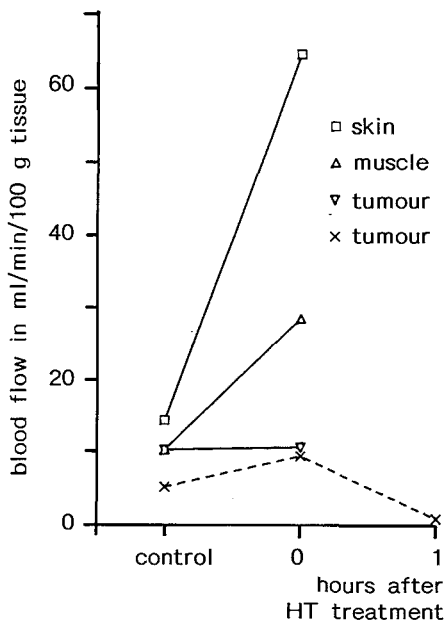


Fig. II - 2 BLOOD FLOW CHANGES

Blood flow changes in skin (□), muscle (Δ) and tumour (∇) during local hyperthermia (1 hour at 43°C) of a Walker 256 carcinoma bearing rat leg. The dotted line shows the blood flow changes in a rat mammary adenocarcinoma (13762A) during and following a similar hyperthermia treatment.

Data from Song et al, 1980A and Rappaport and Song, 1983.

perature increase and the duration of hyperthermia. The initial reaction is an increase of blood flow which, with increasing hyperthermia dose, may be followed by a decrease as a result of damage developed. There is a quantitative difference between this response for normal and tumour tissues. Tumour circulation shows less or no increase during hyperthermia and collapses following lower hyperthermia doses, than normal tissue circulation (Song et al. 1980A; see figure II-2).

The decrease of tumour blood flow following hyperthermia has been observed by many investigators. Reviews of these findings were recently given by Song (1984) and Reinhold and Endrich (1986).

Tumour vascular stasis was observed in some experimental systems already following heat doses as low as 1 hr at 40°C whereas skin and muscle circulation still show an increase following 2 hours at 43-44°C.

Consequences of vascular collapse are that the tumour cell environment changes

towards an increased hypoxia and acidity, which renders the cells even more sensitive to hyperthermia (Bicher et al. 1980), and secondly that cell death continues after the end of hyperthermic treatment as cells become completely isolated from the supply of oxygen and nutrients (Stewart and Gibbs 1984, Fajardo et al. 1980). It is questionable, however, if circulation collapse plays a major role for tumour response following whole body hyperthermia where the temperature should not exceed 42°C.

Hyperthermia in combination with radiotherapy

The survival curve for cells which have received a combined treatment of heat

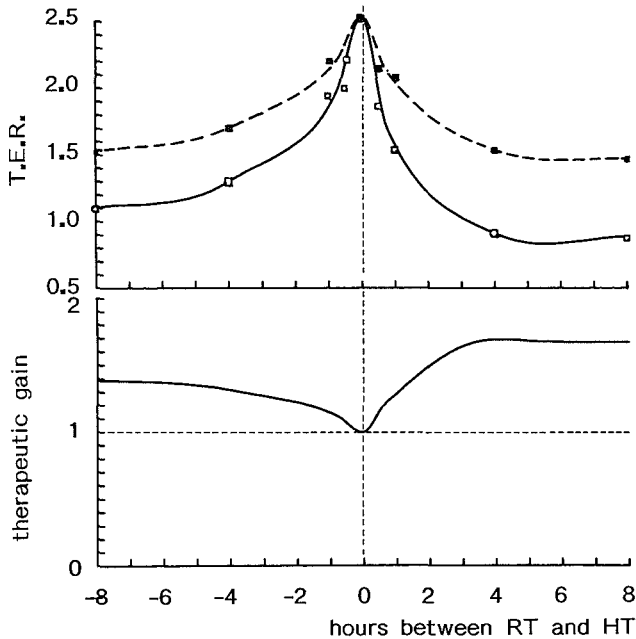


Fig. II - 3 THE INFLUENCE OF THE TIME INTERVAL ON TER

The thermal enhancement ratio (TER) is the factor with which radiotherapy (RT) effect is enhanced by the addition of hyperthermia (HT). This figure shows the TER for both normal tissue (mouse skin, □) and tumour tissue (mouse mammary adenocarcinoma, ■) as a function of time-interval between radiotherapy and hyperthermia (60 minutes at 42.5°C).

When tumour tissue and normal tissues receive the same hyperthermia dose, hyperthermia given 4 hours following radiotherapy gives the maximum therapeutic gain. When however tumour tissue is preferentially heated, simultaneous administration is preferable.

Data from Overgaard, 1980.

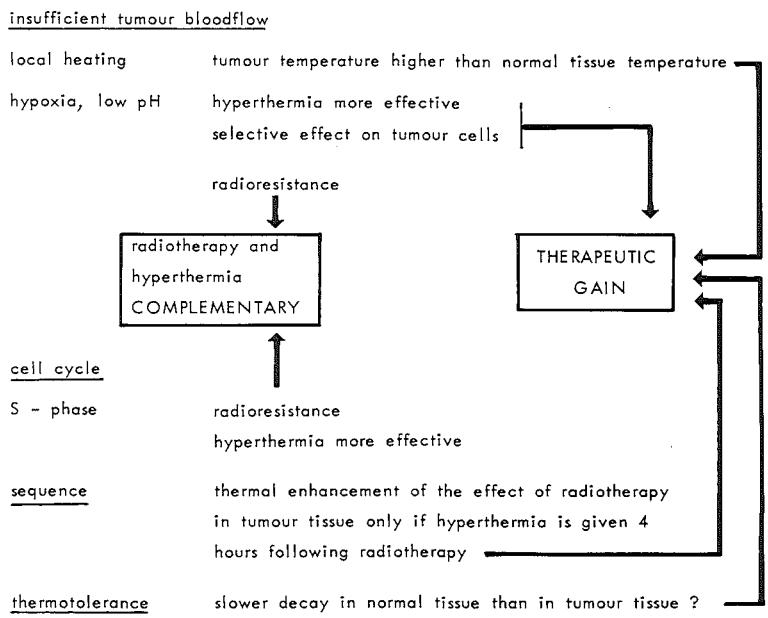


Fig. II - 4 CONCEPTS CONCERNING HYPERTHERMIA IMPROVING LOCAL CANCER TREATMENT

This schedule shows the mechanisms through which hyperthermia, either alone or in combination with radiotherapy, leads to therapeutic gain: a cell killing effect preferentially in tumour tissue.

and radiation has, in comparison with that for cells which have received radiotherapy only, a steeper slope and often also a reduced shoulder (Thrall et al. 1976, Harisiadis et al. 1975, Westra 1971; see figure II-1). It has been demonstrated that hyperthermia decreases the capacity of cells to repair X-ray sublethal and potentially lethal damage (Ben Hur et al., 1974).

Together with these radiosensitizing effects, hyperthermia has an additive effect to that of radiation. As described above, the relatively radioresistant cells in S-phase are more sensitive to hyperthermia. Furthermore, the environmental conditions which occur in tumours, rendering cells more resistant to X-irradiation, enhance the thermal sensitivity of the cells. The sequencing of the two modalities may also be of importance for the effect of the combined treatment. It has been shown in in vitro studies, that when the hyperthermia dose was sufficient to induce thermal killing, hyperthermia preceeding X-irradiation was slightly more effective than hyperthermia following X-irradiation (Sapareto et al. 1978). However, when a lower dose of hyperthermia was given,

which is only sensitizing the radiotherapy effect, hyperthermia following radiotherapy was most effective (Dewey et al. 1977). Overgaard investigated the importance of sequencing in an in vivo system with respect to both tumour response and normal tissue reaction. He found that the largest therapeutic effect was obtained when hyperthermia followed radiotherapy, with a therapeutic gain without enhancement of normal tissue reaction if the time interval was at least 4 hours (Overgaard 1980, see figure II-3). Hume and Field also demonstrated, in various normal animal tissues, that there was no thermal enhancement of X-irradiation when radiotherapy preceded hyperthermia by 4 or 5 hours (Hume and Field, 1978). The mechanisms through which hyperthermia alone and in combination with radiotherapy can lead to therapeutic gain are summarized in figure II-4.

#### Hyperthermia combined with chemotherapy

##### a) Effects on the cellular level.

In vitro studies have shown that the effect of many commonly used cytotoxic agents is enhanced at elevated temperatures. Reviews on this subject were given by Hahn (1979), Marmor (1979) and more recently, Bleehen (1984) and Landberg (1985). Several mechanisms are probably involved in this enhanced cell kill, such as those listed in Table II-2.

There are also several agents which are non-toxic at normothermia, which become cytotoxic at increased temperature such as hypoxic radiation sensitizers, alcohols, local anaesthetics, and solvents for cytotoxic drugs (Landberg 1985, Li et al. 1977). The degree of cell kill enhancement depends not only on the hyperthermia dose, but also on various complicating factors, such as

- the time-sequence of hyperthermia and chemotherapy;
- the history of heat treatment, such as the temperature increase rate or step down heating;
- the cellular environment (hypoxia, pH).

Hyperthermic potentiation of cell killing effect may gradually increase with increasing temperature, but for some agents (for example bleomycin) potentiation was found only above a threshold temperature of 42-43°C which renders the combination unsuitable for whole body hyperthermia (Marmor et al. 1979). For 5-FU a similar threshold temperature may exist, regarding the results of the few studies done with this drug. Mizuno et al. (1980) found no enhanced mouse leukemia cell kill by combining 5-FU with hyperthermia at 42.0°C. Rose et al. (1979) also found no enhancement of 5-FU induced mouse tumour re-

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Table II-2 MECHANISMS INVOLVED IN POTENTIATION OF CYTOSTATIC DRUGS BY  
HYPERTHERMIA

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- Acceleration of chemical processes involved in the action of chemotherapy (a general law in chemical processes).
  - Alterations in cellular membrane functions, resulting in increased cellular uptake (cis Pt (Alberts et al. 1980), adriamycin (Hahn et al. 1975), methotrexate (Herman et al. 1981, Mikkelsen and Wallach 1982)).
  - Increased binding to DNA (cis Pt (Brouwer et al. 1982)), bleomycin (Chapman et al. 1983)).
  - Inhibition of repair processes (bleomycin (Hahn et al. 1975, Kubota et al. 1979)).
  - Inhibition of degradation of the cytotoxic agent (bleomycin (Lin et al. 1983B)).
- 

gression by hyperthermia at 41.5 - 42.4°C, whereas Daly et al. (1982) found a synergistic effect of 5-FU and WBHT at 43°C in the liver of dogs. On the other hand, Lange et al. (1984) report that 5-FU cytotoxicity was enhanced in two human colon adenocarcinoma cell lines at 41.8°C in comparison to cytotoxicity at 37°C, which indicates that treatment of patients with WBHT and 5-FU may be valuable.

For adriamycin and actinomycin D, drug resistance was induced by previous hyperthermia (Hahn and Strande 1976, Donaldson et al. 1978), whereas step-down heating was found to increase potentiation of cell kill for continuing heat treatment at lower temperatures in presence of cytotoxic drugs (Herman et al. 1984).

pH-decrease was found to increase hyperthermic potentiation of cell kill by BCNU and bleomycin (Hahn and Shiu 1983A). Hypoxia enhanced the hyperthermic potentiation of cell kill by mitomycin (Teicher et al. 1981).

Finally, the enhancement of cytotoxic cell kill by hyperthermia appears to be different for various cell lines (Neumann et al. 1985).

b) Effect on the tissular level.

The in vivo situation is even more complex. Drug dosage at the tumour site depends on pharmaco-kinetics, such as distribution, blood flow, metabolism and excretion which may be influenced by hyperthermia (Ballard 1974). It is to be expected that different heating techniques (WBHT, local hyperthermia) will



influence pharmaco-kinetics in different ways. Decreased elimination rates were demonstrated under whole body hyperthermic conditions for melphalan and methotrexate (Hones et al. 1985, Daly et al. 1984), whereas increased intra-tumour concentration was found for melphalan (Hones et al. 1985). Tumour environmental factors are unknown and also may be influenced by hyperthermia. Some but not all drugs which were found to be potentiated in vitro showed potentiation in vivo (Marmor 1979).

The most important question for the clinical situation is, of course, whether therapeutic gain can be achieved, i.e., whether the enhancement in tumour tissue is larger than in normal tissue. This question has been investigated only scarcely.

Therapeutic gain was demonstrated by Dahl and Mella (1982, 1983) for cyclophosphamide and BCNU for a neurogenic tumour in rats with local hyperthermia at 44°C, but could not be found for the same cytotoxic agents by Hones and Bleehen (1982, 1985) for 2 different tumour systems in mice with WBHT at 41°C. Neither was therapeutic gain found for CCNU by Hones in the same mouse system; the only drug with which therapeutic gain was achieved in this system was melphalan, for which bone marrow toxicity decreased, whereas the effect on the tumours was enhanced by a factor 2.5 to 3.9. For cis-Platinum, therapeutic gain was demonstrated by Alberts et al. (1980) in leucaemic bone marrow (vs normal bone marrow) following WBHT at 42°C but Wile et al. (1983) found the opposite in rabbits with carcinoma treated by isolated hyperthermic perfusion at 42°C.

Magin et al. (1980) demonstrated therapeutic gain for adriamycin in mice with mammary carcinoma following local hyperthermia at 43°C.

So far, these findings are not conclusive. The consequence is that clinical application has to be performed very cautiously with either reduced drug dosages or drugs with minor toxicity.



# TECHNIQUES INVOLVED IN THE APPLICATION OF HYPERTHERMIA

## Chapter III

### Introduction

The problem of how to induce hyperthermia cannot be discussed without first discussing some basic thermophysiology. The body temperature is kept within narrow limits. Because the rate of chemical reactions varies with the temperature and the enzyme systems of the body function optimally within narrow temperature ranges, normal body function depends upon a relatively constant body temperature. In order to remain thermal equilibrium, the heat gained by the body must balance its losses. Each violation of this equilibrium will be followed by physiological reactions.

Heat loss to the environment from the skin surface produces a temperature gradient between the core and skin surface (shell). The magnitude of the temperature difference between the various parts of the body varies with the environmental temperature. The core temperature, represented by, for instance, the rectal temperature, is the temperature that varies least with changes in environmental temperature. Understanding of these mechanisms is also important with regard to the decision where to place thermometry probes. (References for the first part of this chapter: Ganong 1971, Ingram and Mount 1975, Nadel 1977 and Emslie-Smith et al. 1983).

## Thermophysiology in man

### A) Mechanisms for heat gain (see table III-1)

Man gains heat mostly from metabolic sources, at rest (basal metabolism, food-induced thermogenesis), during exercise and while shivering.

The most active sites of heat production are the skeletal muscles, the liver and other intra-abdominal organs and the brain.

In cold environments, shivering can increase metabolism. Muscular tone increases in distal parts and this increased tone moves proximally which results in visible shivering. Shivering can increase the metabolic rate by a factor of 2 to 5.

Non-metabolic sources for heat gain are mainly by infrared radiation: short-wave from the sun, long-wave from the surroundings. Ingestion of hot food and drink, ventilation in a hot environment and, during immersion in hot water, conduction of heat can contribute to heat gain.

### B) Mechanisms for heat loss (see table III-1)

The loss of heat from the skin is greatly influenced by environmental conditions such as the ambient temperature, relative humidity and air movements. It also depends on the heat conductance of the skin, depending on skin blood flow.

Heat is lost by convection, radiation, conduction and evaporation. If the subject is in air, the loss takes place mainly by convection and radiation, the amount depending upon ambient temperature and currents in air. Conduction is negligible here. Heat loss by conduction is important during immersion in cold water.

If these passive mechanisms for heat loss are insufficient for maintaining thermal equilibrium, then cooling through evaporation of water becomes an important contribution.

Normally there is an "insensible" water loss which takes place partly through skin; water vapour diffuses continually through the skin without wetting it. Water is also lost from the respiratory tract: water from the mucous membranes of the mouth and the respiratory passages vaporizes in the respiratory air and is lost with each expiration. The amount of the insensible water loss, thus heat loss, depends on the humidity of the environment and the inspired gases, respectively.

Thermoregulatory sweating involves the evaporation of large amounts of water by the eccrine sweat glands. Eccrine sweat glands are capable of producing over 4 litres dilute salt solution per hour. The water in sweat

evaporates on the skin, so reducing the skin temperature, as long as the ambient relative humidity and air current allow such.

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Table III-1 TEMPERATURE REGULATION MECHANISMS

(1) Mechanisms activated by cold

- increasing heat production: shivering
  - hunger
  - increased voluntary activity
  - increased secretion of TSH, norepinephrine and epinephrine
- decreasing heat loss : cutaneous vasoconstriction
  - curling up
  - horripilation

(2) Mechanisms activated by heat

- increasing heat loss : cutaneous vasodilation
  - sweating
  - increased respiration
- decreasing heat production: anorexia
  - apathy and inertia
  - decreased secretion of TSH

Thermoregulatory responses, including autonomic, somatic, endocrine and behavioural changes.

From W.F. Ganong, 1971.

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Thermoregulation

A) Central

The deep body temperature is kept around 37°C with great precision. Both brain damage and various central acting drugs can modify or even abolish normal thermoregulation. These suggest the existence of a central mechanism that is probably localized in the nervous system.

Many hypotheses on thermoregulation have been proposed varying from

relatively simple to exceedingly complicated.

The basic facts are that in and around the hypothalamus three types of nerve cells have been identified: firstly cells which are sensitive for the temperature of the blood perfusing the hypothalamus, secondly cells which, when stimulated, send impulses to organs and tissues involved in the gain or loss of heat and thirdly cells which intermediate between the sensor and activator cells and excite or inhibit the activators. This third group of cells receive impulses from the sensors in the hypothalamus as well as from thermoreceptors in the skin.

Hypothalamic thermoregulation acts as if there were a thermostat and set-point.

#### B) Peripheral

The central mechanism initiates peripheral action, mainly through the autonomic nervous system.

Peripheral thermoregulation is centred on the thermal conductivity of the skin, which is dependent on changes in cutaneous blood flow.

Thermal conductance of the skin of man is defined as the rate of change of heat per °C difference in temperature between that of his body and his surroundings. The thermal conductance can be varied rapidly by redistribution of blood flow. Vasoconstriction reduces the transfer of heat from the core to the surface so that the surface of the skin becomes ischaemic and less heat is lost by convection, radiation and conduction. Cutaneous vasodilatation has the opposite effect. The superficial blood flow may increase to as much as 100 times the minimum flow.

#### Body temperature

A useful concept of body temperature distribution is assuming the existence of a warm, central core within which the temperature remains almost constant and a peripheral shell through which tissues there is a temperature gradient. The temperature gradient between core and skin surface varies by changes in the thermal conductance of the skin by alterations in blood flow, dependent on the ambient temperature and the core temperature. The size of the core, i.e., the area with a temperature of about 37°C, is much larger when the environment of the body is at high temperature than when it is at lower temperature.

Man can influence the ambient temperature, i.e. the temperature directly adjoining the skin, by behavioural actions as clothing and heating.

## Thermometry

During a treatment with whole body hyperthermia, the accurate measurement of temperatures which are representative for the temperature in organs which are especially heat sensitive, is of vital importance.

Two relevant questions are therefore:

- where to measure?
- how to measure?

### 1) Sites of measurement

This first question is related to the temperature distribution in the body. Temperatures of the various tissues vary depending on the rate of metabolism, the efficiency with which the heat can flow away and the distance to the body surface.

During normothermia, or during a steady-state hyper- or hypothermia, the rectal temperature may be regarded as representative for core temperature. The response to change in temperature, however, is relatively slow, which makes the use of rectal temperature less advisable for control during the heating phase.

The temperature in the part of the oesophagus which lies next to the aorta, shows a rapid response to changes of the temperature of the blood coming from the left ventricle and therefore is a better representative for mean core temperature, than rectal temperature.

The tympanic membrane temperature is expected to reflect hypothalamic temperature (Benzinger and Taylor 1963, Cabanac and Caputa 1979), and thus the temperature of the central nervous system. This is important, as the brain may be especially susceptible for heat damage, as brain function disturbances are frequently seen in heat stress victims and brain edema has been observed after WBHT treatments.

Cabanac and Caputa subjected healthy volunteers to heat stress, with or without facial cooling. When facial cooling was applied, the tympanic temperature decreased while the oesophageal temperature increased. An explanation for this finding is that there is a connection between the branches of the facial vein and the cavernous sinus (via the ophthalmic veins, the deep facial vein and the pterygoid plexus), through which cooler blood enters the skull and subsequently cools the brain tissue.

In our case, during the induction of WBHT in the Siemens cabin, the head of the patient is outside the cabin and surrounded by air at room temperature. The situation of facial cooling thus may occur and influence the brain

temperature.

Temperature gradients during WBHT in pigs induced by heating lights, a heating blanket, warmed humidified gases and insulation, were studied by Dickson et al. (1979). They found persistent temperature gradients during the various phases (heating, steady state and cooling) of the WBHT procedure. Temperatures recorded by rectal, deep oesophageal or tympanic membrane probes provided a reliable index of core temperature, including brain temperature during steady-state conditions at 42°C, but the rectal temperature lagged behind the other core temperatures too much to be reliable during the heating phase. The liver temperature was consistently 0.1–0.4°C higher than the rectal temperature, but the difference became less when heating time progressed. The temperatures of the deeply seated sites of the body were always higher than that of the superficial tissues (muscle and subcutaneous fat).

It is clear, too, that the different techniques used for the induction of WBHT results in characteristic temperature distributions. It is therefore important to measure temperatures at multiple (as many as possible) sites during WBHT, because only then it is possible to evaluate the overall temperature distribution, which is of importance with regard to patient toxicity or tumour response.

## 2) Technique

When considering the required characteristics for a thermometry system used in WBHT in combination with local hyperthermia one can list the following prerequisites:

- it should have a relatively small response time (+ 1 second);
- it should have a continuously read out for the critical sites of measurement;
- it should have an accuracy of 0.1°C;
- it should not be disturbed by electromagnetic heating;
- it should be easy to introduce to the site of measurement;
- at least two separate systems should be used independently in order to remain operationally in the case of breakdown of one of the systems.

In order to meet all requirements, four systems were used simultaneously in these investigations:

### 1) The "Ellab" thermocouple system

The essential part of the thermocouples consists of a junction between a copper and a constantan wire. The voltage between the two wires is



temperature dependent. The Ellab Company delivers these thermocouples in probes of many shapes, suitable for various applications.

During our WBHT treatments the following probes were used (see figure III-1):

- rectal (type A-R1): placed in the rectum after bowel emptying;
- oesophageal (type A-OSG): placed in the oesophagus and in the nasopharyngeal space;
- needles (type A-K19 and A-K8), length 3 cms, width 0.5 mm and length 5 cms, width 0.7 mm respectively , for measuring subcutaneous, intramuscular and intratumoural temperatures;
- tympanic (type A-EL2): a flexible probe which was introduced into the outer acoustic meatus against the tympanic membrane, and insulated from the environmental air by a plug of cotton wool;
- flexible small teflon coated probes (type A-F6) for placement on the skin.

These probes were connected to the Ellab Universal Digital thermometer type DU-3.

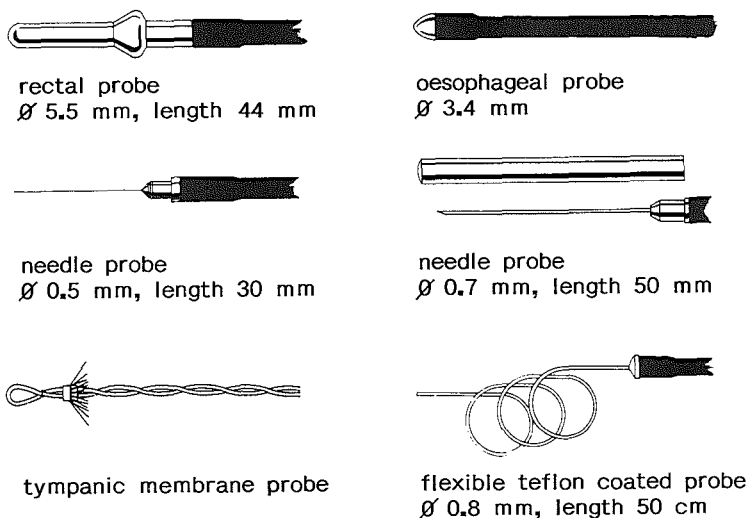


Fig. III - 1 THERMOCOUPLE PROBES USED DURING WBHT

The electronic read out part of the Ellab system was disturbed during the use of electromagnetic energy. With the use of 433 MHz electromagnetic radiation, the needle probes have to be introduced such that the longitudinal axis is placed rectangularly to the electrical field lines in order to avoid heating of the metal. During additional microwave heating, temperature measurements could only be performed with the generators switched off.

In order to ensure continuous control of several critical temperatures at the same time a multiple thermocouple display was developed and built by the Central Research Workshop of the Medical Faculty of the Erasmus University. This was based on a continuing sequential reading out of 10 thermocouple temperatures at the time, each with its separate display. The accuracy of this system is  $0.1^{\circ}\text{C}$ .

2) The Hewlett Packard compact monitor 78341A which we used for cardiovascular monitoring also provided the possibility for temperature measurement, by 2 different thermistor probes. Temperature measurement by thermistors is based on the change in electrical resistance with temperature. The accuracy of this system is  $0.2^{\circ}\text{C}$ . The flexible probe was introduced into the oesophagus in order to have a second temperature control, to avoid a calamity as described by Pettigrew (Pettigrew et al., 1974A). He reported that one patient died as a consequence of an error in temperature measurement which caused an unobserved rise in core temperature up to  $43^{\circ}\text{C}$ .

3) Liquid crystal optical fiber system (LCOF), model LCT-1 of Ramal Inc. Temperature measurement is based on the principle that the absorption of light depends on the temperature of a suspension of liquid crystals. The absorption increases with increasing temperature. The liquid crystal suspension, contained in a small glass bulb and the glass fiber which transports the light is not influenced by electromagnetic heating. It turned out however that the electronic read out part of the system was disturbed by electromagnetic radiation ! A continuous read out was only possible by placing the read out parts in an additional Faraday cage. Disadvantages of this system were the large size of the probes, which renders the impossibility to introduce them into the body, and the chemical degradation of the liquid crystal which makes it necessary to verify the temperature trajects immediately before and after treatment using water baths.

Using this procedure, an accuracy of  $0.5^{\circ}\text{C}$  could be obtained.

This system was used only for measurement of tumour surface temperature

in patient no. 1, in whom WBHT and local hyperthermia were combined.

- 4) A third, independent, system for a reliable measurement of core temperature became available with the monitoring of cardiac output. This measurement is based on the integration of a thermodilution curve following injection of a bolus cold fluid in the pulmonary artery. The build-in thermistor can provide a continuous read out of the pulmonary artery temperature. This thermometry probe has an accuracy of  $0.2^{\circ}\text{C}$ .

#### Techniques for the induction of hyperthermia

Hyperthermia can be applied at 3 levels, i.e.,

- The level of tumour: local (LHT). Only the tumour and the surrounding tissues are heated;
- The level of organ: regional (RHT). The extremity, part of the body, or the organ in which the tumour is situated is heated;
- The level of body: whole body (WBHT). The patient's whole body temperature is increased.

In view of the restricted subject of this thesis, the techniques for application of local and regional hyperthermia will be discussed only briefly, whilst more attention will be paid to whole body hyperthermia.

#### Local hyperthermia

The temperatures which can be achieved in tumours using local hyperthermia are limited by:

- a) the amount of energy which can be deposited in the tumour
- b) the amount of energy which is carried from the tumour, which mainly takes place via blood flow. (See table III-2).

LHT can be achieved by both invasive and non-invasive methods (for a review, see Hand and Ter Haar, 1981, Hand 1981 and Ter Haar 1981). Tumours which extend no more than a few millimeters in depth can be heated by contact application of e.g. hot water (bath or mattress). In clinical practice this is, however, insufficient. The methods which have the greatest potential for inducing local hyperthermia are those in which electromagnetic waves or ultrasound are employed.

In the case of non-ionizing electromagnetic radiation, the level of energy absorbed by tissue depends on the wavelength of the radiation and the dielectric properties of the tissue.

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Table III-2 FACTORS INVOLVED IN TEMPERATURES ACHIEVED DURING  
LOCAL HYPERTHERMIA

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(1) energy disposition

- wave length ~ frequency
- applicator used, coupling to the tissue
- tissue - anatomy
  - dielectric properties

(2) heat dissipation

- blood flow
- thermal properties of the tissues heated
- environmental temperature - adjoining tissues
  - outside the body

Many of these factor unknown for human tissues.

Some of the parameters change with changing temperature.

---

The latter vary according to the wavelength used. Electromagnetic heating can be achieved using radiofrequency (0.5 - 30 MHz) or microwaves (300 - > 1000 MHz). However, the use of electromagnetic waves is restricted, in the absence of a shielded room, to frequencies which are allocated by the government for medical application. In the Netherlands these are 27, 433 and 2450 MHz.

The penetration depth of electromagnetic radiation is defined as the depth at which the power density of a wave has decreased to  $1/e^2$  of its value at the surface. For 2450 and 433 MHz the penetration depths are 1.7 and 3.6 cms in muscle and 11.2 and 26.2 cms in fat respectively. Only superficial tumours can be heated using these two microwave frequencies when radiating sources or contact applicators are used. It is also possible to introduce coaxial applicators into body cavities, e.g., the oesophageal lumen or the bladder. Coaxial applicators with a very small diameter can be introduced directly into tissue. This form of local heating can be very useful when combined with interstitial radiotherapy.

Radiofrequency heating can be achieved using either capacitive or inductive coupling, or localised current fields. For capacitive coupling the tissue to be heated is placed between two electrodes. One of the problems encountered

with this method is that the energy disposition depends mainly on the electrical resistance of the tissue. This makes that, when the two electrodes are placed opposite around the trunk, fat tissues are more easily heated than the underlying tissues with a higher water content. This restricts the possibilities of this system for deep heating.

In inductive coupling, a radiofrequency coil is placed above or around the tissue to be heated. With this method the wet tissues with the highest water content are preferentially heated. The penetration depth of these methods however is small.

Lower frequencies, 100 KHz - 10 MHz, may be used to induce local current fields. These can be applied by electrodes which can be superficially placed, in direct contact with the skin, or interstitially or using a combination of these arrangements. It is also possible to place a cylindrical electrode within the lumen of e.g. the oesophagus and a second, large electrode, externally around the trunk.

It is not possible to obtain homogeneous tissue heating by using any of the methods discussed for local hyperthermia induction. Because energy is absorbed within the tissues, the energy level decreases with increasing depth. Tissue inhomogeneities within the volume to be heated influence the shape of the energy distribution obtained. Local differences in dielectric properties within a tissue type cause inhomogeneities in absorbed energy. Furthermore, the rate at which heat is cleared away from the tissue is of great importance to the final temperature distribution.

It is generally assumed that the blood flow in tumours of a detectable size is lower than that in normal tissue (Jain and Ward-Hartley, 1984). Moreover, an increase in blood flow as a physiological reaction to heat, may occur in a lower rate in tumours than in normal tissues (see chapter II).

In experimental tumours that have, from the clinician's point of view, a small volume (< 2 g), Song observed that the blood flow in the centre of the tumour decreased by 10% following 1 hr. at 43°C, while the blood flow in the surrounding muscle increased by 177% (Song, 1984). As blood flow is the major factor determining the amount of energy carried from tissues, this implies that the application of a homogeneous energy distribution to the tissue, should preferentially heat tumours. All the above mentioned factors concerning inhomogeneous tissue heating, emphasise the necessity of measuring tissue temperatures during local hyperthermia. Thermometry in the presence of electromagnetic fields however presents still considerable problems.

In the first place, metallic thermocouple or thermistor probes within a

needle, suitable for insertion into tissues, interfere with electromagnetic fields. This interference can be minimized in the microwave frequency range, by orientating the probe insertion perpendicularly to the electrical field lines.

Secondly, electromagnetic fields interfere with electronic read-out apparatus. The way to avoid this problem is to switch off the generator for a few seconds during which the temperatures can be read-off. Recently some types of non-perturbing probes have been developed, based on the principles of optical thermometry, using glass or glass like fibers in combination with e.g. liquid crystals or Gallium Arsenide crystals. These probes cannot be inserted directly into tissue, but have to be placed within a catheter.

Ultrasound (0.5 - 5 MHz) can also be used for induction of local hyperthermia. It has to be applied via a coupling medium. Penetration depth is, depending on frequency, 3.7 - 14 cm in fat and 1.4 - 12.5 cm in muscle. The ultrasonic beam has a lower tendency to scatter through the tissue than either microwave or radiofrequency beams have. This characteristic makes it possible to use focussing techniques for heating well defined volumes, and it therefore seems the method of choice. However, serious disadvantages of ultrasound are that it does not penetrate through gas or bone, and that reflections at gas/tissue and bone/soft tissue interfaces occur. As many sites in the body are characterized by the presence of gas and bones, the applicability of ultrasound is therefore limited. Interference-free thermometry can be performed during ultrasound heating using thermocouples. In clinical practice, ultrasound is rarely used.

#### Regional hyperthermia

In regional hyperthermia the entire organ, extremity or region in which the tumour is situated, is heated. Regional hyperthermia has been applied clinically especially for extremities, by perfusion, and bladder and stomach, by irrigation.

Organs or extremities can be heated by isolated perfusion, the relevant artery and vein being connected to a perfusion machine by surgical procedure. Collateral circulation vessels are blocked by externally applied pressure. The perfusate is heated and, in the case of an extremity, the skin is thermally isolated from the environment in order to obtain a more homogeneous temperature distribution. In this way, the heated perfusate heats the tissue which is provided by and drained from blood by the isolated vessel system. This method is often used in combination with cytotoxic agents, which are

added to the perfusate. Tissue temperatures of up to 45°C have been reached in limbs (Cavaliere et al. 1967). Hollow visceral organs can also be heated by irrigation. This has been performed in the urinary bladder and stomach. This method however only achieves an adequate temperature increase over the first few millimeters of the inner surface of the organ wall. Ludgate et al. (1979) mentions a gradient of 1°C per mm tissue in urinary bladder.

Intraperitoneal perfusion can also be performed using heated fluid. Because the surface area heated is very large, heating of the whole body may easily occur. In fact, Priesching (1976) applied peritoneal perfusion in order to obtain whole body hyperthermia.

Deep local heating (non-invasive) can also be regarded as regional heating and it is called as such presently. It is not yet possible to concentrate energy into a deep seated tumour without losing most of the energy to the overlying tissues. Deep local heating of extensive tumours in the thoracic, abdominal or pelvic regions will therefore be accompanied by an increase in the patient's core temperature, the degree depending on the level of energy required and the volume of blood flowing through the region.

Preliminary experience has shown that whole body hyperthermia is more likely to occur during deep local heating in the thoracic region than in the abdominal or pelvic regions (Perez et al. 1984).

#### Whole body hyperthermia

In whole body hyperthermia, the temperature of the patient's whole body is raised. The modern approach is to both introduce thermal energy into the body and reduce heat losses from the patient.

The maximum temperature tolerated lies around 41.8 - 42°C (Pettigrew et al. 1974A). Whole body hyperthermia is the only method with which a homogeneous temperature distribution can be reached within a deep seated tumour, although unfortunately the tumour cannot be heated preferentially, and the tumour treatment temperature is limited to a relatively low level.

#### General considerations

Many methods have been and are still being used to apply whole body hyperthermia. The oldest one is fever induction by administration of bacteria or bacterial toxins, thus causing the patient's thermostat to reset at a higher set-point (Coley 1893, Nauts 1982A).

Before raising the body temperature of a subject, it is useful to compile a heat balance.

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Table III-3 SOME APPROXIMATE VALUES RELEVANT FOR WHOLE BODY HYPERTHERMIA  
TREATMENT OF A 70 kg PERSON\*

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Heat production

Metabolic rate  $300 \text{ kJ}\cdot\text{hr}^{-1}$  (80 Watts)

N.B. The metabolic rate increases about 10% per degree increase  
in body temperature !

Heat loss under normal conditions

via irradiation	60%
via conduction and convection	15%
via insensible perspiration	<u>25%</u>
	100%

Main potential areas of addition heat loss during WBHT:

via perspiration $500 \text{ ml}\cdot\text{hr}^{-1}$	$1200 \text{ kJ}\cdot\text{hr}^{-1}$ (300 Watts)
via i.v. infusions $500 \text{ ml}\cdot\text{hr}^{-1}$	$46 \text{ kJ}\cdot\text{hr}^{-1}$ ( 12 Watts)
via respiration (mainly via moisture)	$100 \text{ kJ}\cdot\text{hr}^{-1}$ ( 25 Watts)

Required for heating (70 kg person)

assuming a specific heat of  $3.5 \text{ kJ}\cdot\text{kg}^{-1}\cdot\text{°C}^{-1}$        $245 \text{ kJ}\cdot\text{°C}^{-1}\cdot\text{hr}^{-1}$

---

\*These approximate values were derived from textbooks (Guyton, 1981; Wright, 1982) and data by Pettigrew and Ludgate (1977) and Volpe and Jain (1982).

Table III-3 indicates the following:

1. Under normal conditions the combined heat loss equals the heat production.
  2. In the case of no heat loss the temperature increases by about  $1\text{°C}\cdot\text{hr}^{-1}$ .
-



Variation in the various physiological parameters between individuals is huge, for example, the metabolic rate between men and women differs substantially. Also temperature regulation mechanisms (sweating, breathing rates) show considerable differences, depending on age, physical condition, body weight, etc. For the purpose of plainness, it must suffice to compile an average based on approximate values (table III-3).

Methods that deposit energy into the body can be divided into two categories - invasive and non-invasive. Techniques are reviewed in table III-4 and figure III-2, including references. In non-invasive methods the energy is applied to the body surface. The energy is then absorbed by the blood and transported through the whole body. The non-invasive techniques that have been employed include: the use of hot air, hot water or wax, either in direct contact with the skin or within bags, mattresses or suits; radiation such as infra-red or

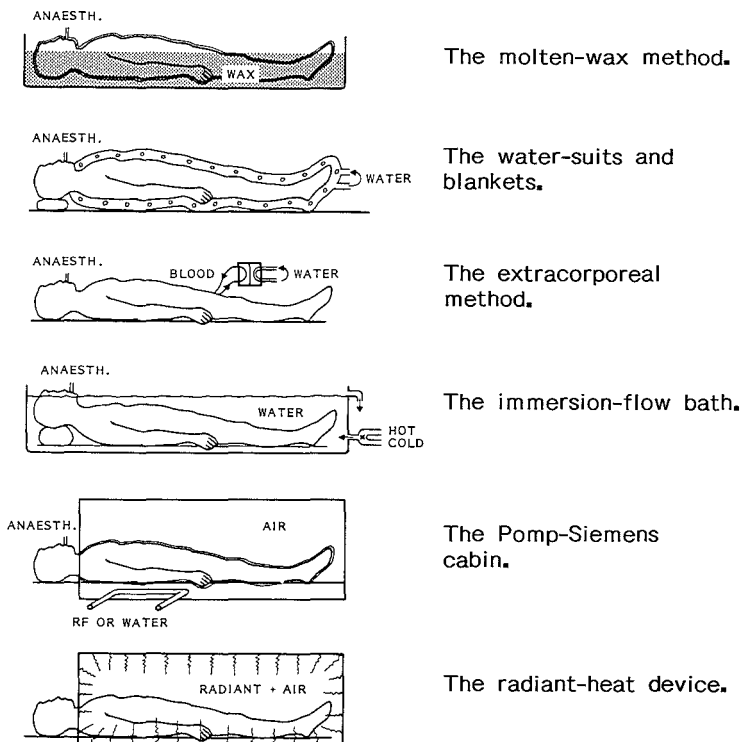


Fig. III - 2 THE VARIOUS WHOLE BODY HEATING DEVICES

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Table III-4 METHODS USED AND IN USE FOR WBHT INDUCTION

TRANSCUTANEOUS

Molten Wax	Pettigrew et al. (1974A and B) (Newcastle) Blair and Levin (1978) (South Africa) Greenlaw et al. (1980A) (Marshfield, Wisconsin)
Water Blanket or Suit	Barlogie et al. (1979) (Houston) Bull et al. (1979) (NCI and Houston) Larkin et al. (1977) (Albuquerque) Moricca et al. (1979) (Rome) Herman et al. (1982) (Tucson) Gerad et al. (1984) (Baltimore)
Infra-red	Heckel and Heckel (1979) (Esslingen/Neckar) Robins et al. (1984) (Madison)
Siemens/Pomp Cabin	Priesching (1976) (Vienna) Pomp (1978) (Hamburg and Essen) Engelhardt et al. (1982) (Freiburg) Van der Zee et al. (present study) (Rotterdam) Kirsch and Schmidt (1966) Dresden Wüst et al. (1975) (Münster)
Waterbath	Von Ardenne (1980) (Dresden) Versteegh (1980) (Leiden)

via EXTRACORPOREAL CIRCUIT

Femoral A-V shunt	Parks et al. (1979) (Jackson, Mississippi) Herman et al. (1982) (Tucson) Lange et al. (1983) (Munich)
Peritoneal irrigation	Priesching (1976) (Vienna)

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electromagnetic radiation; or a combination of two or more of these methods. The immersion of the patient in hot water or wax implies simultaneous blockage of the patient's cooling mechanisms. With the alternative methods, additional isolation is necessary, e.g. with a plastic or aluminium sheet or a blanket.

Invasive techniques for energy deposition are e.g. extracorporeal circulation or, as mentioned before, peritoneal irrigation with heated fluids. The temperature increase that can be achieved by these methods is restricted by the function and thermo-sensitivity of some critical systems, especially of heart and lungs, liver and brain. The maximum tolerable temperature is generally assumed to be  $42^{\circ}\text{C}$ , although treatments at higher temperatures have been reported (Herman et al. 1982, Kirsch and Schmidt 1966, Parks et al. 1979).

In general, if temperatures above  $41^{\circ}\text{C}$  are used, it is preferred to perform the treatment under general anaesthesia. This is necessary for the following reasons. Firstly, the attachment of the monitoring lines necessary for safety control (thermometry, cardiovascular functioning), is unpleasant for the patient.

Secondly, the high body temperature and the resulting tachycardia and tachypnoe makes the patient feel very uncomfortable. Furthermore, to prevent hyperventilation it may be indicated to use artificial respiration.

The drawback of general anaesthesia is that, when no preventive measures are taken, the patient cools rapidly after the initiation of the anaesthesia, before heating is started. This may be not much of a problem when surgery has to be performed, but during a WBHT session this must be avoided in order to minimize the warming-up time.

Energy input can further be increased by heating all infusion fluids, and energy losses can be diminished by warming and humidifying the respiratory gases.

#### Review of WBHT investigations

The earliest report on the use of an external heat supply to induce WBHT is that of Warren, 1935. Warren was impressed by the thought that fever might have a destructive influence on malignant tumours, but decided to develop a simple and safe method for the production of a high body temperature. He used "radiant energy" (incandescent bulbs) as an energy source.

The patient's temperature was maintained at  $41 - 41.5^{\circ}\text{C}$  for 5-21 hours. He gives no information on the use of sedation or anaesthesia, the time required to reach the target temperature, or the toxicity. In 16 of 32 cases with "hopeless malignant disease" treated, the WBHT treatment, in 10 cases combined

with radiotherapy, resulted in marked to moderate improvement: (marked) shrinkage of tumour with (very) slow recurrence.

Hyperthermia, induced by infra-red radiation, was also administered by Heckel (Heckel and Heckel 1979). Clinical indications for treatment with whole body hyperthermia were, in addition to malignant tumours, chronic prostatitis, allergic and rheumatic diseases and epilepsy. The warming-up phase (to 40°C) required about 100 minutes. Forty-six patients, of whom 23 had malignant tumours, received 479 treatments in which the rectal temperature was increased to 39 - 41.4°C. These treatments resulted in the patients with malignant disease in some palliation. Recently, the use of radiant heat was investigated by Robins. The patient lies in a tubular chamber, the wall of which is surrounded by an electric heating coil, with the head outside. When the target temperature is reached, the patient is removed from the coil and covered with blankets to maintain his temperature. Robins achieved a heating rate of about 4.8°C/hour (Robins et al. 1984). The patient is not anaesthetized during the procedure. Recently, Robins reported no toxicity in over 170 treatments at 41.8°C (Robins et al. 1986).

The work of von Ardenne requires particular mentioning. Since 1965 he has performed a great deal of experimental work in support of his proposed cancer multistep therapy (CMT) (von Ardenne and Kruger 1980). CMT is a complicated and theoretical treatment, consisting of a large number of "steps". Some of these "steps" are tumour hyperacidification, achieved by the infusion of glucose, in combination with two-step hyperthermia - whole body hyperthermia at 40.5°C and additional local hyperthermia at 42.5°C.

Von Ardenne claims that his treatment schedule results in irreversible occlusion of tumour vasculature by stiffened erythrocytes. He speculates that the stiffening of erythrocytes is the consequence of changes in rigidity of the erythrocyte wall, brought about by the pH reduction resulting from glucose infusion. This is followed by secondary damage to the tumour cells. In many of his publications a complicated schedule for the simultaneous administration of WBHT, radiotherapy, cytotoxic agents glucose, vitamins and other therapeutic measures is described.

In 1966 Kirsch, who was inspired by von Ardenne, reports his investigations on whole body hyperthermia (Kirsch 1966). He started off testing various techniques on dogs, and found that heating by hot waterbaths was less toxic than heating by extracorporeal blood heating methods: more dogs survived the former method at mean temperatures of up to 43.9°C.

Based on these experiments he started the clinical application of whole body

hyperthermia. The patient was anaesthetized and placed in a waterbath at 45°C with the head lying in an adjacent cold bath for selective cooling of the head. Only once in a series of 120 treatments was a serious complication observed. This consisted of a cardiac arrest, which occurred during hyperthermia, but this was reversed by (immediate) cooling. Kirsch reports that he was able to maintain the patient's temperature at 44°C for 30 minutes with no serious toxicity. Nevertheless, in view of the poor condition of most of his patients, he decided to restrict treatments to 42°C for one or more hours. Waterbath heating was later clinically investigated by Versteegh (1980). He achieved a temperature increase of 6.0°C/hour. This meant that the warming-up period (to 42°C) was restricted to less than 1 hour. He observed no serious toxicity following 10 treatments in 4 patients.

In 1969 the first, very concise, report on the Pomp-Siemens cabin appeared (Pomp and Franz 1969). In this cabin hot air, radiofrequency and microwave energies can be used simultaneously to heat the patient. In 1978 Pomp reported that a core temperature of 40 - 42°C could be reached within half an hour (Pomp 1978). Seven of these cabins were placed in various clinics in Europe. A review (Reinhold et al. 1980), shows that the warming-up time varies from 25 to 130 minutes, depending on the target temperature chosen and the use of the various built-in energy sources. The cabin has been used by Pomp, Priesching, Wust, Engelhardt, Moricca, Dietzel and Wallach. At this time the cabin is still being used by Engelhardt's group in Freiburg.

The use of paraffin wax for energy input was introduced by Pettigrew (Pettigrew et al. 1974A). The patient is anaesthetized and artificially ventilated, sealed in a plastic bag and placed in a bath. Molten paraffin wax, heated to 50°C, is then pumped around the patient. The body heating rate with this method is 3 - 6°C/hour, depending on body weight. The part of wax that is still in the liquid state when the oesophageal temperature reaches 41°C, is removed, leaving the solidified wax around the body as an insulating layer. The patient's temperature can be controlled by varying the area of skin exposed to the air. This technique was later used by Levin and Blair (1978) and Greenlaw et al. (1980A). Levin & Blair used a modification of Pettigrew's technique; the wax was applied within plastic bags, which had the advantages of causing less spillage of wax and enabling the removal of all the wax, so that the patient could be managed more easily during subsequent irradiation.

In addition to the use of the Pomp-Siemens cabin, Priesching (1976) also investigated hyperthermic peritoneal perfusion. When the peritoneal perfusate is heated to 45°C, the warming-up time required (to 42°C) was 2 - 2.5 hour.

He preferred to use peritoneal perfusion in patients with peritoneal metastases, because selective tumour heating could be achieved in nodules smaller than 5 mm diameter.

Many investigators use hot water, either in blankets or suits, as a caloric source. The most important reports of this method are by Larkin et al. (1977), Morrica et al. (1979), Bull et al. (1979) and Barlogie et al. (1979). Using this method a core temperature of 42°C can be achieved within 2 hours. In general, the patient is anaesthetized.

A method which has relatively recently come into use is that of extracorporeal circulation, with direct heating of the blood. For this method an arteriovenous shunt must first be constructed. During the warming-up phase the blood is heated to 45°C by a heat-exchanger in the extracorporeal circulation. The maintenance of the target temperature can be automatically regulated. With this method, the oesophageal temperature can be increased to 41.5°C in as little as 22 minutes (Parks et al. 1979), although Lange et al. (1983) report a warming-up time, to 41.8°C, of 60 - 120 minutes.

In 1976, when the investigations on applicability of WBHT in the Rotterdam Radiotherapeutic Institute were started, only few of the above mentioned experience was published. The Pomp Siemens cabin appeared to offer some major advantages such as continuous visual control of the patient, easy patient care and possibilities for simultaneous local heating. The experience with this system is described in the following chapters.

# INITIAL RESEARCH

## Section II





# DEVELOPMENT OF THE ADAPTED POMP-SIEMENS CABIN METHOD

## Chapter IV

### History

From September 1976 animal experiments were performed in order to learn to know the optimal use of the cabin and to get some experience with the heating of living bodies. This investigation was done mainly on dogs. Later on, the experiments with dogs were extended with measurement of brain temperature and intracranial pressure during WBHT.

In 1978 some experience was obtained with temperature measurements in human patients undergoing fever therapy induced by the injection of *C. parvum* in the Antoni van Leeuwenhoek Hospital in Amsterdam. A visit paid to Dr. Ollendiek in his private hyperthermia clinic in Bad Neuheim, Germany, revealed some of the practical problems encountered with the clinical administration of WBHT.

In June 1978 the first patient was treated in Rotterdam. Until patient 10, the heating method was adjusted on the basis of experience obtained.

### The Pomp-Siemens cabin

The Pomp-Siemens hyperthermia cabin consists of a bed-like structure covered by a semi-cylindrical perspex hood. The construction is schematically represented in figure IV-1.

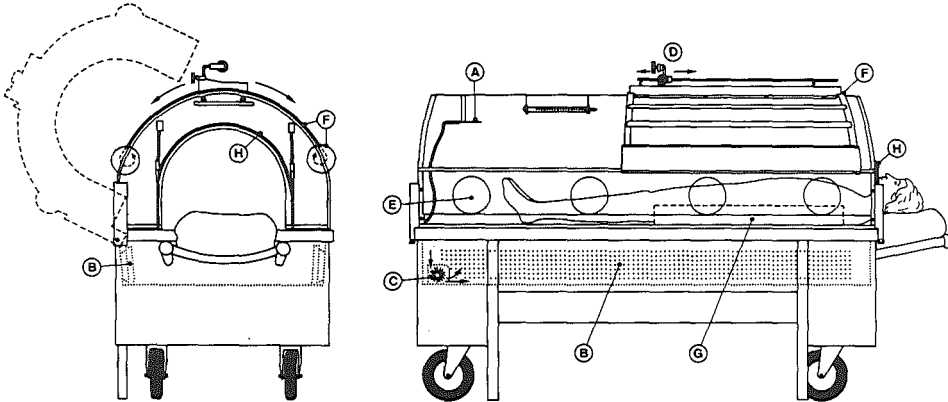


Fig. IV - 1 THE POMP-SIEMENS HYPERTHERMIA CABIN

The Pomp-Siemens hyperthermia cabin. Size of the main body (without head rest), 187 cm long and 92 cm wide. (A) Sensor for thermostat; (B) air heating elements; (C) axial ventilator (not shown in left diagram); (D) adjustable holder for microwave applicators (applicators not shown); (E) ports for handling infusions, etc (sliding doors not shown); (F) adjustable plastic roller top; (G) place for radiofrequency coil under patient; and (H) holder for sealing cloth.

In the head end of the hood an opening is provided through which the patient's head can be positioned outside the cabin. There is a holder around this opening to allow sealing of the area between the patient's neck and the edges of the opening. There are ports laterally in the wall of the hood, through which handling of infusion and monitoring lines is possible.

These ports can be closed by sliding doors. The cranial part of the hood has a plastic roller top, which can be opened for manoeuvring the microwave applicator holder system.

The hood can be opened by hinges placed laterally. This was changed by us by the construction of a lifting tackle, with which the hood could be removed vertically, allowing the approach of the patient from both sides.

There are three sources of energy which can be used to heat the patient.

#### 1) Air system

Between the mattress on which the patient is positioned and the sides of the cabin is a space of about 10 cm. This area is covered by an appropriately shaped plywood board with slits. In the area below the level of the mattress, two 1.2 kW electrical air heaters are located on each

side. The hot air rises through the slits and surrounds the patient. The air is recirculated through a long axial ventilator located below the foot end of the lower air space. Thermostatic control is provided by a sensor located in the upper part of the dome of the hood. The temperature of the air within the cabin can be read off from an alcohol thermometer located in the same area as the thermostatic control sensor.

2) Radiofrequency system

In the mattress, on which the patient lies, a single flat loop of a radiofrequency coil (size about 40 x 50 cm) is incorporated horizontally at the level of the patient's torso. This coil can be connected to a 27 MHz generator, delivering maximally 400 W.

3) Microwave system

A microwave applicator can be manoeuvred within the cabin such that microwave energy can be directed to most sites of the ventral upper part of the body. There are three types of antennas available, which can be connected to a 433 MHz generator, which can deliver up to 250 W.

With the heating equipment available, we were faced with the following questions to be answered:

- which of the 3 heating systems, e.g. warm air, radiofrequency and microwave, or which combination, would provide the highest heating rate and at which levels of energy output;
- how would the use of any combination influence the temperature distribution;
- how easy would the temperature control be with the equipment, for example at the end of the heating phase (overshoot should be avoided at any price!) and during the plateau phase;
- in which amount would the use of electromagnetic energy disturb the temperature and physiology monitoring lines and, if this would be not acceptable, could this disturbance be avoided ?

To answer these questions, a series of dog experiments was performed. This also made it possible to investigate organ toxicity following WHHT at various levels.

## Animal experiments

### I Investigation of operational aspects and heating capacity of the cabin and general toxicity of WBHT in dogs

This part of the study is based on the raw data obtained by the group when it consisted of Mrs. L. Bonke-Spit, Drs. A. Felijs and Ing. G.C. van Rhoon.

Ten mongrel dogs of either sex (body weight 23-37, mean 30.0 kg, age 2-5 years) were subjected to 45 experiments, including 5 control and 40 heating sessions.

Anaesthesia was induced in fasted animals by intramuscular injection of ketamine and vetranquil (4.5/0.5 ml) and maintained using smaller doses.

If tachycardia (heart rate > 180) occurred a  $\beta$  blocker (propranolol hydrochloride 1 mg; Inderal ICI Ltd) was given. The dogs were intubated to prevent excessive cooling via the tongue by panting (which is the main cooling mechanism in dogs), but were allowed to breathe spontaneously. Following intubation the ECG was connected and an intravenous catheter was established for the infusion of fluids (0.45% NaCl/2.5% glucose).

Temperature measurements were performed in the rectum during each experiment. Other sites for temperature measurements were the oesophagus

(n = 25), the external acoustic meatus (n = 25), intramuscularly (n = 31) and subcutaneously (n = 31). For these measurements the Ellab thermocouple system as described elsewhere (chapter III) was used. When electromagnetic heating was used temperature data were collected with the generator switched off.

Hyperthermia was induced in the Pomp Siemens cabin using one of or a combination of the three techniques: warm air, temperature 30 - 70°C, 27 MHz radiofrequency and 433 MHz microwaves, as is indicated in table IV-3. The rectal temperature strived for during the hyperthermia experiments was  $40.5 \pm 0.2^\circ\text{C}$  (n = 3),  $41.0 \pm 0.2$  (n = 4),  $41.5 \pm 0.2$  (n = 14),  $42.0 \pm 0.2$  (n = 12) and  $42.5 \pm 0.2^\circ\text{C}$  (n = 6) respectively. This temperature generally was maintained for two hours. In one dog accidentally an overshoot in core temperature up to 44°C occurred.

Blood samples were taken before the start of treatment and afterwards immediately and at 24 hour time intervals up to 4 days after treatment.

## Results

### A) Evaluation of the heating technique

#### 1) Thermometry

During 25 heating experiments, rectal as well as oesophageal and tympanic membrane temperatures were measured. The maximum value of each of these

temperatures was considered to be indicative for the safety level of treatment. These maximum levels, and the differences between these values are given in table IV-1.

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Table IV-1 THE HIGHEST TEMPERATURES MEASURED DURING WBHT IN DOGS AT THE VARIOUS LEVELS, AND THE DIFFERENCES BETWEEN THE TEMPERATURES MEASURED AT THE VARIOUS CORE SITES

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	<u>range</u>	<u>mean</u>	<u>s.d.</u>
rectum	40.6 - 42.5	41.81	0.44
oesophagus	40.6 - 42.4	41.76	0.44
tympanic membrane	39.9 - 42.2	41.41	0.51
$\Delta(T \text{ oesophagus} - T \text{ rectum})$	- 0.6 - + 0.2	- 0.05	0.17
$\Delta(T \text{ tympanic membrane} - T \text{ oesophagus})$	- 1.0 - + 0.3	- 0.35	0.27
$\Delta(T \text{ tympanic membrane} - T \text{ rectum})$	- 1.1 - 0	- 0.4	0.22

---

The mean difference between rectal and oesophageal maximum temperature of  $0.05^{\circ}\text{C}$  is negligible. Besides, in 23 of 25 experiments, the difference was less than  $0.2^{\circ}\text{C}$ . The tympanic membrane temperature is considerably lower than rectal or oesophageal temperature. This difference with oesophageal and rectal temperature was less than  $0.2^{\circ}\text{C}$  in only 7 and 4 experiments respectively. In only 1 experiment the maximum tympanic temperature was higher than oesophageal temperature.

The rate of temperature increase, in  $^{\circ}\text{C}$  per hour, varied from 0.9 to 5.8 and from 0.8 to 2.5 for rectal and oesophageal temperature respectively. The value of  $5.8^{\circ}\text{C}/\text{hour}$  was observed in a dog in which a high level of energy was introduced by 27 MHz radiofrequency, resulting in, at the start, a very high temperature in the superficial tissues and, despite ending energy input, an overshoot of rectal temperature up to  $44^{\circ}\text{C}$  with as a result the death of the dog. In this dog no oesophageal temperature was measured. This experiment was excluded from analysis, leaving a maximum value for rectal temperature increase of  $3.1^{\circ}\text{C}$  per hour. This experience learned us to avoid local high energy input during subsequent experimental and clinical WBHT treatment.

In 25 experiments the rectal as well as the oesophageal temperature was recorded. In 3 experiments there was no difference between the rate of temperature increase. The rate was higher for rectal than for oesophageal temperature in 4 and the opposite was found in 18 experiments respectively. The difference varied from - 0.1 to 0.5°C per hour with the oesophageal rate being mean 0.12°C (s.d. 0.15) per hour higher than the rectal rate. When at the end of the heating period the energy input is decreased, the lead of oesophageal temperature is rapidly overtaken by rectal temperature.

## 2) Efficiency of heating method

Rectal heating rate was found to depend not only on technique used, but also on the body weight of the heated animal. This is demonstrated in table IV-2, where the heating rates are given for two levels of cabin air temperature. The heating rate for dogs with a body weight below 30 kg is for both air temperatures higher than that for dogs weighing more than 30 kg. The efficiency of the heating method used can therefore be established by dividing the rate of temperature increase by the body mass to be heated, i.e., the body weight in kg.

As rectal temperature was measured during each of the experiments and there was a significant correlation between rate in increase of temperature in the oesophagus and in the rectum ( $r = 0.937$ ;  $p < 0.001$ ), only

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Table IV-2 RECTAL HEATING RATE IN DOGS IN RELATION TO BODY WEIGHT

<u>air temperature (°C)</u>	<u>body weight (kg)</u>	<u>n</u>	<u>heating rate (°C/hr)</u>	
			<u>mean</u>	<u>sd</u>
45 - 55	< 30	6	1.40	0.09
	> 30	4	1.10	0.18
55 - 70	< 30	8	2.16	0.43
	> 30	4	1.70	0.08

Heating was achieved by the use of warm air only.

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the rectal temperature increase rate was used in this analysis. The mean's and s.d.'s for rectal temperature increase rate per kg. body weight for each of the heating methods is represented in table IV-3. The highest value was obtained using high cabin air temperature ( $> 55^{\circ}\text{C}$ ) only, although there is no significant difference with the value obtained using cabin air at  $35\text{--}45^{\circ}\text{C}$  in combination with 27 and 433 MHz electromagnetic heating.

The body weight was found to be related square to temperature increase rate. As heating is performed through the skin surface and the ratio body mass to skin surface decreases with increasing body weight, this relationship is not surprising.

In figure IV-2 the relation between temperature increase rate per kg. body weight and the body weight in kg. is presented for the experiments in which an air temperature of  $> 45^{\circ}\text{C}$ , whether or not in combination with local 433 MHz heating, was used. The correlation coefficient of these data

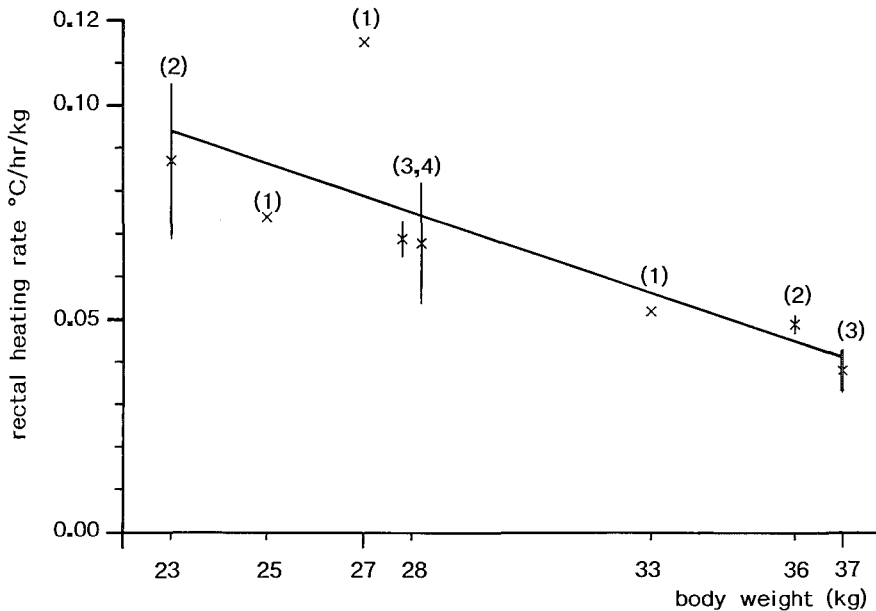


Fig. IV - 2 RECTAL HEATING RATE IN DOGS; ARRANGED TO BODY WEIGHT

Rectal heating rate ( $^{\circ}\text{C}/\text{hour}/\text{kg}$  bodyweight) for 8 individual dogs, arranged in order of body weight. This figure shows the means, standard deviation and the regression line. The number of data available for each dog is given in parenthesis.

Table IV-3 RECTAL HEATING RATE PER KG BODY WEIGHT IN DOGS FOR THE VARIOUS TECHNIQUES USED

air temperature (°C)	27 MHz	433 MHz	n	heating rate (°C/hr/kg)	
				mean	sd
< 35	+	+	1	0.043	-
35 - 45	+		6	0.045	0.013
	+	+	3	0.068	0.032
		+	2	0.057	0.006
45 - 55			10	0.042	0.011
55 - 70			12	0.070	0.023
		+	5	0.053	0.019
		+	17	0.065	0.022

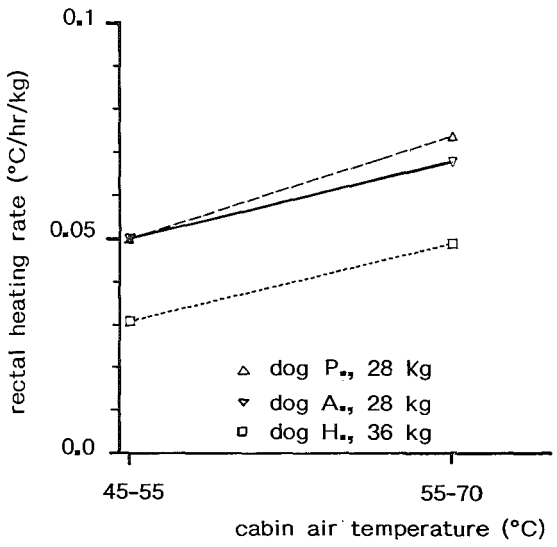


Fig. IV - 3 RECTAL HEATING RATE IN DOGS

Rectal heating rate (°C/hour/kg body weight) in three individual dogs, obtained with warm air only at two different temperature levels.



was found to be  $-0.776$  ( $2p < 0.05$ ).

In three dogs it was possible to compare the mean values for rectal temperature increase rates at two different heating techniques: air temperature of  $45-55^{\circ}\text{C}$  and  $55-70^{\circ}\text{C}$  respectively. These values are given in figure IV-3. The dog with a body weight of 36 kg is considerably slower with increasing rectal temperature than the dogs of 28 kg, but the increase in rate with a higher level of energy applied is equal.

### 3) Temperature distribution

The differences between the temperatures measured at sites representative for core are discussed above.

The difference between the maximum temperature for any location in the shell, i.e., intramuscular or subcutaneous, and the maximum rectal temperature varied from  $-0.3$  to  $+3.7^{\circ}\text{C}$ . The core-shell differences were compared for the heating methods including and without the use of electromagnetic radiation respectively.

The mean difference between rectal temperature and highest shell temperature for heating with hot air only was  $0.24^{\circ}\text{C}$ , SEM  $0.06$  ( $n = 21$ ). The mean difference for the methods including electromagnetic heating was  $1.15$ , SEM  $0.27$  ( $n=15$ ). The highest differences were seen when 27 MHz radiofrequency heating was used. These results indicate that heating with hot air only provides the best temperature homogeneity.

### 4) Interference of electromagnetic (E.M.) radiation with monitoring equipment

Interference occurs when the monitoring read-out systems pick up the E.M. radiation waves, and becomes a serious problem when the energy of the E.M. signal is so high that the signal given by the monitoring probe cannot be distinguished.

Electric apparatuses used during the WEHI experiments include:

- the HP compact unit for monitoring ECG, respiration and core temperature;
- the Ellab DU3 thermocouple read-out system;
- the Ramal liquid crystal fiber optic (LCOF) read-out system;
- a 4-channel recorder.

Interference was observed for each of these apparatuses. Interference could be prevented only for the LCOF read-out system, which probe is transparent for E.M. radiation, by isolating the read out system within a

Faraday cage. Continuous monitoring of vital parameters, however, was impossible during the use of electromagnetic heating.

### Conclusions

During the heating phase the monitoring of both oesophageal and rectal temperature is necessary for a safe administration of whole body hyperthermia. The difference between the maximum value of both temperatures is negligible which can be explained by the rapid gain of rectal to oesophageal temperature after the energy input is decreased when nearing the set-point. During steady state the control of rectal temperature provides safety.

The finding that the highest value for temperature increase rate was obtained using hot air only, combined with the observations that the temperature distribution is inhomogeneous and the electronic monitoring equipment is disturbed when electromagnetic heating is used, points towards the choice for the clinical heating method: hot air only. In patients with a superficial tumour on the ventral part of the body, 433 MHz local heating may be administered additionally during steady state periods.

### B) Toxicity of WBHT in dogs

Four dogs died following WBHT treatment. In three cases this was following WBHT at maximum levels of rectal temperature of 41.6 to 42.5°C. In the fourth dog, this was caused by failure of the heating method. In this case, radiofrequency power was used during the heating phase up to the maximum level possible. This resulted in a very high rectal temperature increase rate (5.8°C per hour, body weight 27 kg). Rectal temperature continued to increase, even after the generator was switched off and cooling with ice cubes was started, up to a maximum value of 44°C. This must have been caused by a very high local temperature increase in the tissues close to the radiofrequency coil and a redistribution of energy by the bloodflow after switching off the generator. One hour after the rectal temperature started decreasing, heart and respiration stopped. Reanimation attempts were without success. Post mortem examination showed disseminated intravascular coagulation throughout the whole body. From this experiment it was concluded that WBHT at 44°C implicates the risk of lethality in dogs.

Two dogs died shortly after termination of the WBHT treatment. One dog

treated with a heat dose of  $2\frac{1}{2}$  hours above  $41^{\circ}\text{C}$ , maximum rectal temperature  $41.6^{\circ}\text{C}$ , became comatous and died on the evening following WBHT. Gross post mortem examination did not reveal the cause of death. The second dog was treated for  $2\frac{1}{2}$  hours above  $42^{\circ}\text{C}$ , maximum rectal temperature  $42.5^{\circ}\text{C}$ . One hour after cooling was started, the dog became comatous; inspection of the retinae revealed excavation of the papillas, indicating brain oedema.

A fourth dog died 5 days after WBHT,  $2\frac{1}{2}$  hours above  $42^{\circ}\text{C}$ , maximum rectal temperature  $42.2^{\circ}\text{C}$ . This dog was treated with anticoagulants in order to prevent DIC, from 3 days before WBHT till the time of death. Cause of death was shown to be haemorrhage in the mediastinum.

In all dogs, post mortem examination of the brains (Prof. Stefanko, Medical Faculty of the Erasmus University Rotterdam) showed aspecific changes in brain tissue. The total weight had increased to 85 - 90 g (from a normal weight 75 g), red blood cells were found perivascularly and small foci with haemorrhage and/or DIC were seen. These findings were most consistent with brain oedema, which might have contributed to the death of the dogs.

#### Circulatory and respiratory changes

Heart rate increased during WBHT up to maximum 153% of its starting value (mean rate at  $t = 0$ , mean temperature  $38.6^{\circ}\text{C}$ , was 119 beats per minute). The heart rate increased with 14 beats per minute with each  $1^{\circ}\text{C}$  temperature increase (see figure IV-4). The correlation coefficient for the relation between temperature and heart rate was found to be 0.847 ( $2p < 0.05$ ).

Respiratory rate increased enormously up to 20 times its starting value (mean respiratory rate at  $t = 0$  was 27). As dogs cool by increasing the air flow over the tongue, this phenomenon is not expected to occur at the same amount during patient treatments. The respiration rate also appears temperature dependent, see figure IV-4. The correlation coefficient of this relation was found to be 0.982 ( $2p < 0.001$ ). During plateau phase (the phase of steady state WBHT at the planned level) changes in acid-base balance were observed. pH shifts to higher values with increasing temperatures whereas  $\text{pCO}_2$  dropped (figure IV-5). The acidosis expected on the base of the increased metabolism during hyperthermia appears to be compensated by the increase in respiration.

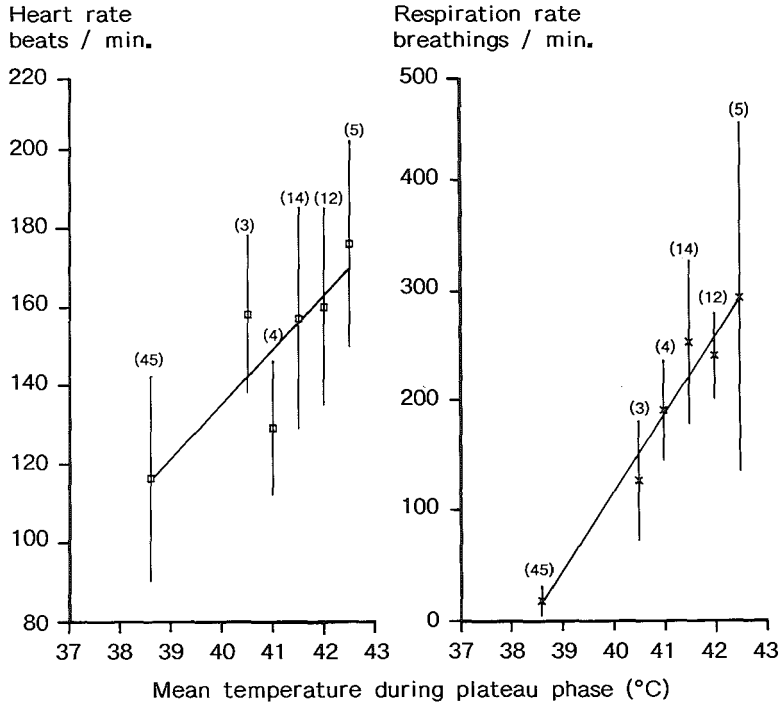


Fig. IV - 4 HEART RATE AND RESPIRATION RATE DURING WBHT IN DOGS

In this figure the means and standard deviations are shown for each hyperthermia level. The number of data available for each temperature is given in parenthesis.

Laboratory

The important changes are given in table IV-4. Some of the most important findings will be discussed below, grouped according to the type.

Electrolyte changes

There were no changes in  $\text{Na}^+$  and  $\text{Cl}^-$  blood values.  $\text{K}^+$  dropped to minimum 83-88% of its normal value only after WBHT at temperatures above 41.3°C.  $\text{Ca}^{++}$  showed minor decreases also after the control experiments. These electrolyte changes were maximum within 24 hours following WBHT. As sweating, causing loss of electrolytes, is not part of the cooling mechanism in dogs, electrolyte changes after human WBHT may be expected to be of greater importance.

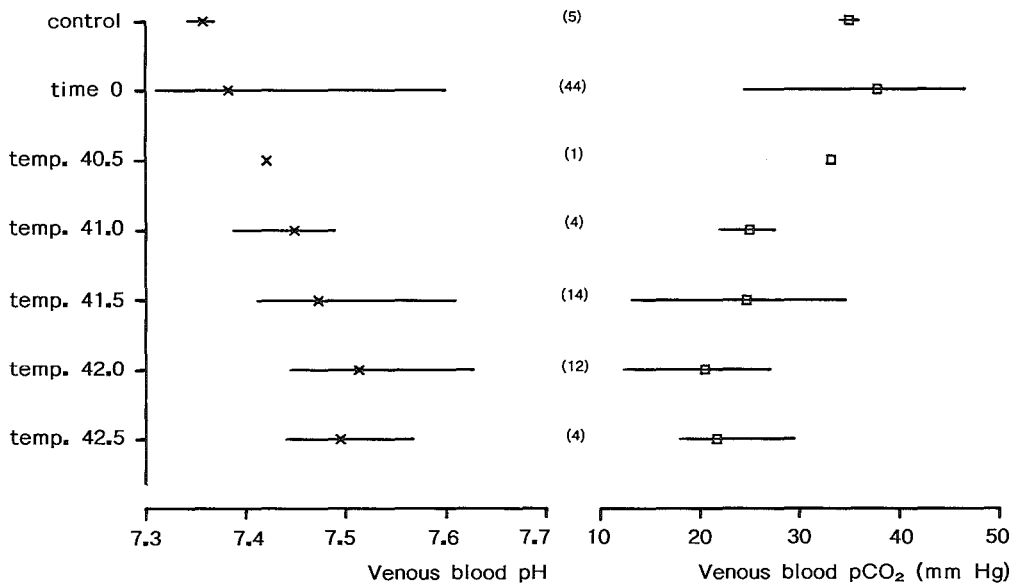


Fig. IV - 5 ACID - BASE BALANCE CHANGES DURING WBHT IN DOGS

Means and ranges for venous blood values of pH and pCO<sub>2</sub> during WBHT (plateau phase) in dogs, at various levels of hyperthermia dose. The number of data available for each temperature level is given in parenthesis.

#### Haematology and coagulation

The number of leukocytes increased up to 262% of the normal value, the maximum was reached usually after 24 hours.

The number of platelets decreased to 47 and 13% of the starting value after WBHT at  $42 \pm 0.2$  and  $42.5 \pm 0.2^{\circ}\text{C}$  respectively. The decrease following WBHT at temperatures lower than  $42^{\circ}\text{C}$  was less obvious; the number of platelets stayed within the range of normal value.

Disseminated intravascular coagulation (DIC) was observed in one of the dogs that died; the phenomenon was not diagnosed in the surviving dogs on the basis of laboratory changes. Although fibrinogen degradation products (FDP) increased up to almost a factor 8 higher than the starting value, fibrinogen showed no consistent decrease.

#### Liver damage

Liver damage was judged according to changes in the enzymes SGOT, SGPT,

Table IV-4 MAXIMUM CHANGES (IN % OF STARTING VALUE) OF VARIOUS PHYSIOLOGICAL PARAMETERS FOLLOWING WBHT IN DOGS

temperature (°C)	starting values		control	WBHT TREATMENT, TWO HOURS EXPOSURE				
	38.6		38.7	40.5 ± 0.2	41.0 ± 0.2	41.5 ± 0.2	42 ± 0.2	42.5 ± 0.2
	n=44		n=5	n=3	n=4	n=14	n=12	n=5
	mean	sd	mean %	mean %	mean %	mean %	mean %	mean %
Heart rate	119	26	-	153	132	136	141	149
Respiratory rate	27	13	-	633	1082	1224	1066	2028
Total Ca (mmol/l)	2.39	0.009	95	-	93	93	-	97
K <sup>+</sup> (mmol/l)	4.17	0.45	-	-	-	83	83	88
alk.phosphatase (U/l)	40.5	55.9	-	-	-	377	714	2456
SGOT (U/l)	23.7	13.3	406	284	1018	949	1083	1615
SGPT (U/l)	52.7	53.4	-	-	282	439	528	964
LDH (U/l)	113	65	276	-	-	260	-	-
Urea (mmol/l)	6.3	1.3	-	-	-	-	146	-
Leucocytes (10 <sup>6</sup> /l)	5439	1313	167	147	140	162	214	262
Platelets (10 <sup>9</sup> /l)	223	94	-	-	-	-	47	13
Fibrinogen (g/l)	1.51	1.22	-	-	-	-	-	-
FDP (mg/l)	52.7	52.8	447	344	400	547	670	775

Changes are only reported when they exceed the range of starting values.

LDH and alkaline phosphatase.

SGOT and SGPT increased with increasing plateau temperature, the latter showing increase from a treatment level of 40.8°C. For both enzymes a dose-effect relationship was indicated. These changes may be ascribed to liver damage as well as to damage to other organs.

LDH showed no important changes, even at the highest treatment level.

Values for alkaline phosphatase showed significant increases only after treatment temperatures of 41.3°C. Enzyme levels had returned to normal within 96 hours following WBHT.

#### Kidney function

As there were no changes in creatinine blood levels up to the highest level of WBHT (42.5 ± 0.2°C), the kidney function seems not to be influenced by the treatment procedure. Blood urea value was increased by 46% only in the group of WBHT at 42 ± 0.2°C, but this elevation most likely reflects tissue damage.

#### Conclusions

The experimental WBHT treatments in dogs learned that WBHT up to 42.5°C is tolerated by these animals without major toxicity on most organ systems. The demands on the cardiovascular and respiratory system are large as demonstrated by an increase in heart and respiratory rates; patient selection should therefore include investigation of the capacity of both systems. Considerable liver damage has been reported after WBHT at temperatures above 41.5°C (Pettigrew 1974B, Levin and Blair 1978) but no irreversible damage was observed in these experiments.

Brain oedema was observed in 4 dogs for which the experiment ended fatally. This finding urged us to perform further experiments. These experiments, which were carried out in the course of 1 year and which in time overlapped the clinical study, will first be discussed in this experimental section.

## II Measurement of cerebral temperature and epidural pressure during WBHT in dogs.

In this study 13 beagles of either sex (body weight 8-12 kg, age 1-2 years) were used.

Anaesthesia and ventilation measures were equal to those in the first

series of experiments.

Following intubation the ECG was connected, and to enable pressure monitoring catheters were introduced into the common carotid artery and the femoral vein. The catheters were connected to Hewlett Packard model 1280 C pressure transducers and an appropriate readout apparatus. An i.v. catheter was established for the infusion of fluids:

0.45% NaCl-2.5% glucose;  $0.13 \pm 0.06$  l/hr (mean  $\pm$  1 SD). The skin over the skull was incised and the parietal bone cleared of overlying muscle and fascia, then a hole was drilled on each side of the skull, approximately 1 cm from the midline, taking care not to damage the dura. The epidural pressure was monitored with a microtip pressure transducer (Millar Mikro-Tip, model PC-370). It was zero balanced at  $38.5^{\circ}\text{C}$  or  $40.0^{\circ}\text{C}$  prior to each experiment. Zero drift was 0.05kPa (0.4 mmHg) per hour, and temperature drift was 0.05 kPa per  $^{\circ}\text{C}$ .

This pressure monitoring system was made available to us by H. Kameraat and P. van der Kemp, dept. of Medical Electronics, Zuiderziekenhuis Rotterdam, and the technique by Prof. C.J.J. Avezaat and dr. J.H.M. van Eindhoven, depts. of Neurosurgery and Neurology, Medical Faculty, Erasmus University Rotterdam.

The transducer was inserted 1.5-2 cm through the hole (diameter 7-10 mm) on the right-hand side of the skull and was carefully positioned between the dura and the skull with its sensitive tip resting against the dura (figure IV-6).

The temperature measuring system (Ellab DU-3) was calibrated to an accuracy of  $0.1^{\circ}\text{C}$  against a  $0.05^{\circ}\text{C}$  precision mercury thermometer (Eichamt für Glasmessgeräte Darmstadt, FRG). Needle thermocouples (Ellab AK19, diameter 0.5 mm), for cerebral and epidural temperature measurements, were inserted via the same hole as was used for the pressure transducer (see figure IV-6). The thermocouple for the epidural measurements was rounded at the tip and preshaped to the measuring site. The hole on the left-hand side of the skull had a diameter of only 2 mm and was used solely for the insertion of a second intracerebral thermocouple. The intracerebral thermocouples were inserted in both hemispheres to a depth of 3.0 cm in the first six dogs and 1.5 cm in the other six. One dog in the control group had no thermocouples inserted into the brain. After placement of the probes the cranial defects were closed with bone wax. In all cases the



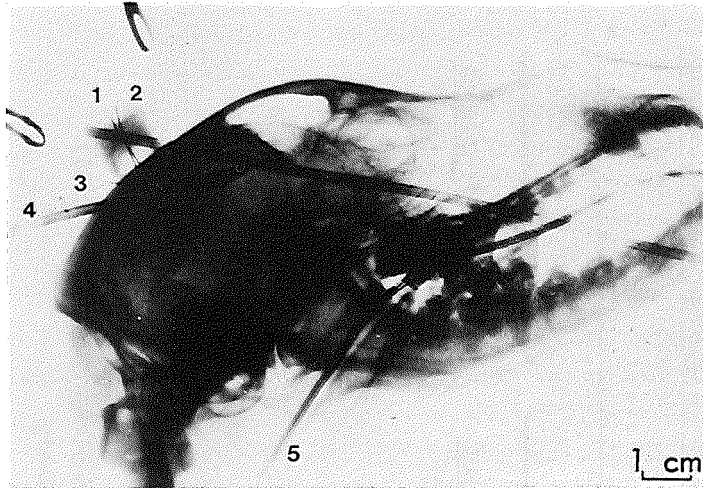


Fig. IV - 6 BRAIN TEMPERATURES AND EPIDURAL PRESSURE DURING WBHT IN DOGS

This X-ray shows the brain thermocouples (1,2,3), the oesophageal thermocouple (5) and the pressure transducer (4) in position.

rectal and oesophageal temperatures were measured. The rectal thermocouple was inserted to a minimum of 5 cm, and the oesophageal thermocouple was placed in the lower third of the oesophagus. To induce hyperthermia the dog was then placed in a cabin in which hot air ( $60^{\circ}\text{C}$ ) was circulating. The animal was positioned on its left side, with its head outside the cabin, so that the head was not being exposed to the hot air. These preparations required about 3 hours, then the heating commenced and after another 2-3 h the planned rectal temperature was attained. This temperature could be maintained by adjusting the temperature of the air circulating in the cabin. The animal was held at plateau temperature for at least 2 hours unless it died earlier due to respiration problems. Temperature and pressure measurements were taken every 10 minutes.

### Results

Of the six dogs with cerebral thermocouples inserted to a depth of 3.0 cm, only two completed the 2 h at the planned maximum rectal temperature. The other four developed respiration problems, three dogs before the start of plateau and one dog during the plateau period. These respiratory problems probably had been caused by damage inflicted by the needle to the neuro-

Table IV-5 TEMPERATURES IN ANAESTHETIZED, INTUBATED DOGS DURING A 2-H PERIOD OF WHOLE-BODY HYPERTHERMIA

Location	Plateau period					
	Start		1 hr		2 hr	
	<u>Heated</u> (n=7) <sup>b</sup>	<u>Control</u> (n=2) <sup>c</sup>	<u>Heated</u> (n=6) <sup>b</sup>	<u>Control</u> (n=2) <sup>c</sup>	<u>Heated</u> (n=6) <sup>b</sup>	<u>Control</u> (n=2) <sup>c</sup>
Rectal	42.1 ± 0.82	38.9	42.2 ± 0.59	39.3	42.3 ± 0.32	39.1
Oesophageal	42.2 ± 0.85	39.0	42.6 ± 0.54	39.4	42.6 ± 0.51	39.1
Cerebral left	42.5 ± 0.81 <sup>a</sup>	39.2	42.6 ± 0.45 <sup>a</sup>	39.8	42.7 ± 0.44	39.4
Cerebral right	42.4 ± 0.78	39.2	42.4 ± 0.55	39.8	42.6 ± 0.44	39.4
Epidural	42.0 ± 1.2	38.5	42.2 ± 0.48	38.9	42.2 ± 0.35	38.6

The data presented are the mean ± 1 SD in °C

<sup>a</sup> The paired mean difference with the rectal temperature is statistically significant (2p < 0.05)

<sup>b</sup> The number of measurements for the oesophagus is 6, 5 and 5, respectively

<sup>c</sup> One of the control dogs had no intracerebral thermocouples inserted

logical respiration control system; we observed no further respiratory problems when the insertion depth of the needles was limited to 1.5 cm. It was decided that use of the data collected up to 20 min before start of respiration problems was justified, as no influence upon the course of the treatment before this point could be seen, and once problems arose they developed very rapidly. All six dogs with cerebral thermocouples 1.5 cm deep and the one dog with no cerebral thermocouples completed the experiment without problems. The mean rate of temperature increase was  $2.3 \pm 0.55^{\circ}\text{C}/\text{h}$ . At normotemperature,  $38.0\text{--}39.0^{\circ}\text{C}$ , there were significant ( $2p < 0.05$ ) differences of 0.8 and  $0.3^{\circ}\text{C}$  between the rectal and the cerebral temperature at depths of 3.0 and 1.5 cm, respectively, on both the right and left hand side of the brain. The difference of  $0.5^{\circ}\text{C}$  between the cerebral temperature at 3.0 and 1.5 cm depth, measured in different animals, is also statistically significant ( $2p < 0.05$ ). As the temperature increased this difference became smaller. Once the plateau temperature had been reached only the cerebral temperature on the left-hand side at 1.5 cm depth was still significantly higher ( $0.4^{\circ}\text{C}$ ) than the rectal temperature. The oesophageal and epidural temperatures were within the range of the rectal temperature. The paired mean differences with the temperature for the various measuring sites at the start of plateau, and after 1 and 2h at plateau are shown in Table IV-5.

For each point in time the data for heated dogs are given on the left, and on the right the control values for two dogs with a temperature below  $40^{\circ}\text{C}$ . The different plateau temperatures were of no influence on the gradients obtained. The left-hand side of the brain was consistently  $0.4^{\circ}\text{C}$  higher than the rectal temperature. This difference is statistically significant (Student's t-test,  $2p < 0.05$ ) during the first 90 min of plateau. The temperature on the right-hand side of the brain was also higher than the rectal temperature, but the difference ( $0.3^{\circ}\text{C}$ ) is not significant. The mean oesophageal temperature was higher than the rectal temperature, but this difference was highly dependent upon correct positioning of the oesophageal probe. Table IV-6 summarizes the results of the epidural and arterial pressure measurements performed on all dogs. The pressures given are: at a rectal temperature of  $38.5^{\circ}\text{C}$  (reference), dogs heated for 2 hr, and two control dogs that were sham-treated for 2hr. The mean epidural pressure remained within normal values during the whole treatment session, in all dogs, irrespective of temperature and treatment time, although the mean diastolic epidural pressure decreased by a factor of nearly 2 ( $0.99 \pm$

Table IV-6 EPIDURAL AND ARTERIAL PRESSURE IN DOGS DURING WHOLE-BODY HYPERTHERMIA

	Plateau period							
	Normal	Start		1 hr		2 hr		
			Heated	Control	Heated	Control	Heated	Control
Temp. ( $^{\circ}$ C)	38.5	42.1 $\pm$ 0.8	38.9	42.2 $\pm$ 0.6	39.0	42.3 $\pm$ 0.3	39.0	
Press. (kPa)								
Epidural								
syst.	1.51 $\pm$ 0.36	1.75 $\pm$ 0.49	1.93	1.57 $\pm$ 0.52	1.80	1.36 $\pm$ 0.49	1.87	
diast.	0.99 $\pm$ 0.32	0.75 $\pm$ 0.39	1.27	0.47 $\pm$ 0.25	1.27	0.49 $\pm$ 0.31	1.47	
mean	1.16 $\pm$ 0.33	1.08 $\pm$ 0.42	1.49	0.84 $\pm$ 0.34	1.45	0.78 $\pm$ 0.37	1.60	
Arterial								
syst.	12.0 $\pm$ 1.2	12.4 $\pm$ 1.9	11.7	11.3 $\pm$ 2.8	12.0	10.8 $\pm$ 2.3	12.1	
diast.	8.6 $\pm$ 1.3	6.2 $\pm$ 2.9	6.9	4.3 $\pm$ 2.0	8.1	4.7 $\pm$ 1.9	8.3	
mean	9.73 $\pm$ 1.3	8.3 $\pm$ 2.6	8.5	6.6 $\pm$ 2.3	9.4	6.7 $\pm$ 2.0	9.6	
n=	7	7	2	6	2	6	2	

The data presented are the mean  $\pm$  1 SD in kPa

1 kPa = 7.5 mm Hg

n= number of measurements

0.32 kPa to 0.49±0.31 kPa). This effect was, however, in close correlation with the change in the mean diastolic arterial pressure, which decreased by the same factor. The mean systolic arterial pressure remained at a normal level (Van Rhoon and Van der Zee 1983).

### Conclusions

In dogs, WBHT, with a rectal temperature of up to 42.5°C for 2 hours, obviously does not cause an increase in epidural pressure during the treatment time.

The initial cerebral temperature is somewhat higher than rectal and oesophageal temperature respectively, but the differences while apparently still existing, are no more statistically different during the plateau phase.

Cooling of the part of the head exposed to the surrounding air appears to influence cerebral temperature as demonstrated by the consistent higher temperature in that side of the brain on which the dog was lying.

The oesophageal temperature appears to reflect the brain temperature better than rectal temperature.

### Temperature measurements in some patients under hyperthermic conditions

This part of the study is based on the data obtained by the group when it consisted of Mrs. L. Bonke-Spit, Drs. A. Felius and Ing. G.C. van Rhoon.

In order to obtain experience in the measurement of temperatures in patients under hyperthermic conditions, we took the opportunity given to us by Dr S.P. Israëls from the Antoni van Leeuwenhoek Ziekenhuis in Amsterdam and by Dr Ollendiek from the Bristol-Klinik in Bad Nauheim, to attend and to participate in patient treatments.

#### 1) Temperature measurements during C.parvum fever therapy

In the Antoni van Leeuwenhoek Hospital, a study was performed on the effects of fever therapy, induced by C. parvum, in combination with melphalan.

The first patient in whom we participated in the treatment was a 57-year-old female with a 14-month-history of malignant melanoma, previously treated with chemotherapy by isolated perfusion, cryosurgery, radiotherapy and surgical removal of lymph node metastasis. Pretreatment status included multiple subcutaneous metastasis with no evidence of metastasis elsewhere.

The second patient was a 35-year-old male with a 22-month-history of malignant melanoma, previously treated with surgery of the primary tumour and various metastasis and immunologic therapy by BCG scarification. The pretreatment status included multiple subcutaneous and lung metastasis.

In both patients *Corynebacterium parvum* was administered by intravenous infusion lasting 35-45 minutes. Temperature increase was observed 60-90 minutes after the start of infusion. Patient 1 was insulated using blankets; in the second patient aluminium foil and an electrical heating blanket were used.

Melphalan 50 mg was injected intravenously in both patients at oesophageal temperatures of 40.3 and 40.8°C respectively. A temperature above 40°C was maintained for a period of 195 and 145 minutes in the first and second patient respectively.

In both patients temperatures were measured in the oesophagus, the rectum, the acoustic meatus and subcutaneously. In patient 2 an additional intramuscular temperature was measured.

Temperatures were measured using the Ellab medical thermocouple system, described elsewhere in this thesis. (chapter III).

Characteristics of temperature increase are given in table IV-7.

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Table IV-7 CHARACTERISTICS OF TEMPERATURE INCREASE DURING *C. PARVUM* FEVER THERAPY

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Site of temperature measurement	T max(°C)		time to reach 40 °C (min) from start increasing T		time above (min) 40°C	
	Pt 1	Pt 2	Pt 1	Pt 2	Pt 1	Pt 2
oesophagus	40.8	40.8	40	50	195	145
rectum	40.8	41.0	85	75	195	200
external acoustic meatus	40.5	40.3	55	95	165	75
subcutaneously	38.9	38.3	-	-	-	-
intramuscular	-	39.2	-	-	-	-

---

The oesophageal temperature increases the most rapid, followed by the temperature in the external acoustic meatus in patient 1 and the rectal temperature in patient 2 with a delay of 15 and 25 minutes respectively. In both patients the maximum temperature in the external acoustic meatus is lower than the oesophageal and the rectum temperatures. The shell temperatures, measured intramuscularly and subcutaneously remain, despite of insulating, far below  $40^{\circ}\text{C}$  in both patients. The use of aluminium foil and a heating blanket seems to give no benefit.

The treatment procedure was tolerated reasonably well by both patients. Toxicity included severe pancytopenia in patient 1 and leukopenia and moderate temporary liver disturbances, established by an increase in liver enzyme levels, accompanied by icterus, in patient 2.

In patient 1 a 3 weeks lasting tumour regression of 30-40% was observed. In patient 2 no effect was observed.

## 2) Temperature measurements in a patient treated in a peripheral clinic

Dr Ollendiek in his private Bristol-Klinik in Bad Nauheim, treats patients with WEHT, in combination with stimulation of the immune system by thymus-abstract and, in most cases, endoxan.

The anaesthetized patient is heated using a mattress perfused with water at a temperature of  $46^{\circ}\text{C}$ . The patient is insulated using an electrical heating blanket in combination with aluminium foil. Ollendiek standard only measures oesophageal temperature by a thermistor. Additional measurements were performed by us with Ellab thermocouples in the rectum, the external acoustic meatus, subcutaneously and intramuscularly. When the oesophageal temperature reaches  $41^{\circ}\text{C}$ , the watertemperature in the mattress is decreased to  $40^{\circ}\text{C}$  and the heating blanket is switched off. At an oesophageal temperature of  $41.4^{\circ}\text{C}$  part of the body surface is exposed to room temperature. The oesophageal temperature is maintained at  $41.5 \pm 0.5^{\circ}\text{C}$  for 5 hours with heating by the electrical blanket and cooling by exposing body surface to room temperature. After this period the patient is cooled by flowing of cold water through the mattress, blowing air over the skin and wetting the skin. The rate of temperature increase should depend on body weight. The weight of the patient in whom we measured was 65 kg, the temperature increase was  $1.5^{\circ}\text{C}$  per hour. In two other patients with a weight of 50-60 kg, treated at the same time in the same room, the temperature increase was  $\pm 2.3^{\circ}\text{C}$  per hour.

The desired temperature level during plateau phase can be kept constant

relatively easily with this method. The increase in oesophageal temperature was, again, the most rapid: 40°C was reached in 95 minutes. The rectal temperature was second to reach 40°C : 100 minutes. The acoustic meatus, subcutaneous and intramuscular temperatures reached 40°C after 110, 120 and 120 minutes respectively.

The temperature distribution within the body was rather homogeneously: with maximum achieved temperatures of 41.8°C for oesophagus, rectum and muscle, 41,5°C for subcutaneous tissue and 41.2°C for the external acoustic meatus respectively. The time above 41°C varied from 210 (acoustic meatus) to 275 (oesophagus) minutes.

### Conclusions

The above described experience can lead only to some tentative conclusions. Fever therapy provides a relatively slow temperature increase, up to levels which are considered insufficient to cause cell death. The temperature distribution is very inhomogeneous with a core-shell temperature difference as large as 1.6 - 2.7 °C. Dr Ollendiek's method provides a better WBHT treatment with regard to heating rate, hyperthermia dose and homogeneity of temperature respectively. With both methods, oesophageal temperature increase is faster than rectal temperature increase. This finding stresses, again, the importance of monitoring oesophageal temperature during the heating phase.

### The Rotterdam patient series

During the patient series, the treatment set-up and scheduling was adapted on the basis of experience obtained. This was particularly of importance with regard to the policy on additional local heating and on additional treatment with other treatment modalities.

### Additional local hyperthermia

The original design was to induce whole body hyperthermia by hot air up to a level which was tolerated by the unanaesthetized patient and was safe with regard to normal tissue tolerance, and to administer additional heating by 433 MHz to the site of the tumour.

This approach had completely changed after the third treatment of the first patient. This first patient was a 53-year-old female, with locally recurrent breast cancer. There was an extensive tumour involvement of the homolateral



thoracic wall, surrounded by a zone of cutaneous carcinomatous lymphangitis. Conventional therapy of all kinds had been given previously and was exhausted. The first WBHT treatment was given to a maximum rectal temperature of  $40.5^{\circ}\text{C}$  with the patient sedated, combined with additional electromagnetic heating of the tumour mass on the chest wall. The whole procedure took over 8 hours. The patient felt uneasy, suffering palpitations and shortness of breath and she stated the treatment unbearable. It was decided to give subsequent treatments under general anaesthesia.

The second treatment included a maximum rectal temperature of  $41.4^{\circ}\text{C}$  and a maximum tumour temperature of  $43.8^{\circ}\text{C}$ , obtained under general anaesthesia, and yielded no problems.

During the third treatment session, however, a very rapid increase in tumour temperature suddenly occurred; resulting in the development of a severe third degree burn of the thoracic wall, including necrosis of an area of rib cartilage. The cause of the sudden high temperature increase may have been a standing wave, by reflection on underlying ribs, or a stoppage of the local circulation effected by the hyperthermia dose administered to the region. As it is known now, the temperature distribution within an area heated with electromagnetic radiation may be very inhomogeneous and the development of a local hot spot can not be ruled out by the, clinically limited, number of temperature measurements. If the patient had not been anaesthetized, she would have no doubt warned that the local temperature increase was much too high. It was decided to never again use local hyperthermia by electromagnetic heating in an anaesthetized patient unless better temperature monitoring systems should be developed.

#### Management of heating technique

During subsequent treatments, WBHT was induced using warm air at  $60 - 65^{\circ}\text{C}$  only. During the first WBHT treatment in patient no. 4, the heating rate was relatively low ( $1.4^{\circ}\text{C/hr.}$ ). This was ascribed to the excessive sweating manifest in this patient. At that time the sweating was attempted to be restrained by the administration of high dosages of atropin.

It was realised then that this cooling mechanism would inevitably play a heating rate limiting role during induction of WBHT in each patient. It was decided that from that time on, cooling by evaporation of sweat was to be prevented by wrapping the patient in plastic foil.

Later during the treatment series, when it appeared that the heating rate remained relatively low, it was realised that energy transport to the body

would become much more efficient when not only the ventral part but also the dorsal part of the skin surface would be used as heat exchanger. From patient no. 10, a mattress with circulating warm water became part of the heating equipment; properly this mattress replaced the original 27 MHz radiofrequency coil. With these two adjustments, the "adapted Pomp-Siemens cabin method" was completed.

#### Addition to other treatment modalities

From the beginning, the concept was that hyperthermia up to 42°C by itself would not be able to destroy all tumour cells. When it was observed in the first three patients that, in the case that tumour regression could be induced (in patient 2 and 3 of 50 and 20% respectively), it lasted for only a few weeks and thus was no real benefit to the patient, it was decided to combine WBHT with either chemotherapy or radiotherapy. The combination with radiotherapy was considered to be most promising, based on the data as described in the thermobiology chapter.

When the patient had previously received radiotherapy, with curative intention, the additional radiation dose to be given in combination with WBHT was necessarily limited to 15-20 Gy. In four not previously irradiated patients the radiotherapy dose was also limited to about 20 Gy: two patients with mesothelioma who received irradiation of one whole lung including mediastinum and two patients with a large abdominal tumour who were treated preoperatively with the combination of WBHT and radiotherapy.

During WBHT selective tumour cell killing can not be expected on the base of selective tumour heating but rather on the differences in physiology between tumour and normal tissue. Therefore WBHT treatment has to be given in a way that radiotherapy effect on normal tissue is not enhanced. This selective enhancement of radiotherapy in tumour tissue only has been obtained experimentally by giving the two treatment modalities with a time interval of at least 4 hours (Overgaard 1980). The most practical solution for achieving this condition was to omit the radiation treatment at the day of the WBHT session.

In 5 patients WBHT was given in combination with chemotherapy. The knowledge on the combination of hyperthermia with chemotherapy was, and still is, very limited, especially with regard to the in vivo situation. Criteria for the choice of an antitumour agent were that toxicity should be relatively mild and that effectiveness should have been demonstrated against the specific tumour type in clinical studies. This resulted in the choice of Melphalan for patients with breast carcinoma who had been treated before with chemotherapy,

and of 5 fluoro-uracil for patients with colon or lung adenocarcinoma. These agents were administered by intravenous infusion at the moment that a rectal temperature of 41,0°C was reached. In order to avoid unexpected toxicity, it was decided to give reduced dosages only of these drugs.



# THE CLINICAL TREATMENT

## Section III



# MATERIALS AND METHODS

## Chapter V

### Criteria for selection

In 1978, when the first patient was treated with WBHT, there was hardly any information on toxicity to be expected, nor on measures to prevent toxicity. There were only few published reports on the clinical results of WBHT induced for cancer treatment. The variation of reported techniques of heating, anaesthesia, temperature level and treatment duration was extensive so that it was by that time not possible to draw a conclusive protocol in which toxicity would not appear. A summary of toxicity following WBHT reported in the period 1974-1980 is given in table V-1. The other possible source of reports of heat toxicity, i.e. the publications on the syndrome of heat stroke mostly lacked important information such as the body (core) temperature of the patients and the exposure time.

The data obtained in the experiments with dogs provided some guidelines but could not be directly translated into safe levels of hyperthermia in humans, since thermophysiology is different in humans and dogs. In general one might expect that the sensitivity of the whole body to heat must be higher than that of its composing elements, i.e., cells, proteins, etc.

The following was taken into account for the planning of pretreatment evaluation and treatment.

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Table V-1 REPORTED TOXICITY WITH WBHT

<u>cardiovascular system</u>	hypotension electrolyte disturbances capillary leak syndrome with pulmonary oedema* brain oedema* cardiac arrhythmias and/or arrest*
<u>organs</u>	disseminated intravascular coagulation* respiratory failure* liver failure* decubitus peripheral neuropathy diarrhoea

\* reported lethality

Data from Greenlaw et al. (1980B), Priesching (1976), Pettigrew et al. (1974A), Larkin et al. (1977), Moricca et al. (1979), Bull et al. (1979).

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### Cardiovascular system

The cardiovascular problems as observed in heat stroke are due to a complex of factors. Dehydration in combination with a redistribution of blood flow to the skin causes hypotension (Costrini et al. 1979), followed by failing oxygenation of the tissues. During controlled whole body hyperthermia treatment, dehydration can be prevented by the infusion of fluids, and blood pressure can be controlled by volume replacement and use of drugs.

Priesching (1976) described two fatal complications in a series of 28 patients because of impairment of circulation.

Pettigrew et al. (1974A) observed fatal ventricle fibrillation in 1 patient in whom core temperature had increased up to 43°C.

Larkin et al. (1977) found a 15% incidence of cardiac arrhythmias, ventricular in origin, in 58 treatments. These were occasionally difficult to control with usual doses of anti-arrhythmic agents, such as xylocain, and in one case cooling and cessation of the treatment was required.



As mentioned in chapter IV, in the experiments with dogs the cardiovascular system was found not to be the limiting factor at temperatures up to 42.5°C. The heart rate in dogs increased with mean 14 beats min<sup>-1</sup> with each 1°C increase in temperature.

It was decided that only patients with good cardiac function would be eligible for treatment with WBHT.

#### Respiratory system

The oxygen requirements increase with increasing temperature. In heat stroke, hyperventilation with resulting respiratory alkalosis is a common symptom (Sprung et al.1980). Pettigrew et al. (1974B) describe how two children with an advanced form of cancer died shortly after WBHT treatment due to respiratory complications. They were given opiates for relief of distress which may have depressed respiration and so contributed to the fatal outcome.

Another one of his patients died of fibrosing alveolitis, possibly due to the use of hot moist ventilating gases and impairment of the pulmonary surfactant system. Priesching (1976) describes four patients developing lung oedema, of whom one died. This complication seems to be more frequent in patients with carcinomatous lymphangitis (Larkin, personal communication 1979).

Larkin et al. (1977) observed lung atelectasis, once progressing to pneumonia, in a few of their "early cases", heated in a heat chamber without artificial ventilation. This complication was not seen in the series treated under general endotracheal anaesthesia.

As mentioned in chapter IV, it was observed in the dogs that the respiration rate increased from 20-30 at normotemperature to a mean value of 303 per minute at the highest hyperthermic level. As hyperventilation is known to be a cooling mechanism in dogs, and not in humans, this finding has no consequences for clinical WBHT.

It was concluded that only patients with a good lung function would be considered for WBHT treatment and that during and following WBHT treatment, lung function had to be controlled by serial gas analysis.

#### Central nervous system

Heat stroke can be accompanied by confusion, desorientation, coma, delirium and/or convulsions (Marty and Samii 1983). Part of this syndrome can be explained by electrolyte disturbances, which are often seen following heat stroke as well as WBHT (hypocalcaemia, hypophosphataemia, hypomagnesaemia; Sprung et al.1980, Larkin et al 1977, Barlogie et al.1979, Herman et al.1982).

In a publication on ten lethal heat stroke victims, Chao et al (1981) describe how the brain in 8 out of 9 patients investigated showed histopathological changes such as local haemorrhages, thrombi and congestion.

In two patients in Priesching's WBHT series brain oedema was fatal (Priesching 1976). Death followed after a period of organic psychosyndrome, based on acute brain cortex degeneration. These patients both had received WBHT in combination with hyperglycaemia of 24 hours duration and multi-chemotherapy, which makes conclusions on the precise cause of toxicity impossible. Another of Priesching's patients died when acute necrosis of a subarachnoidal located metastasis of malignant melanoma ensued, resulting in intracerebral haemorrhage.

Moricca et al. (1979) observed brain oedema in two patients. Dr. Ollendiek (personal communication 1978), who has been treating many patients first in Bad Homburg and later in the Bristol Clinic Bad Neuheim, Germany, also observed lethal brain complications, which might have been oedema as well as haemorrhage in a metastasis; in his hospital no pathohistologic studies were performed.

As described in chapter V, four dogs in our first series of animal experiments that had died showed aspecific pathology of the brain. The weight had increased and the histology resembled oedema. There were also signs of intravascular coagulation.

A second series of experiments with dogs was performed later. Intracerebral temperature and epidural pressure was measured during WBHT. In contrast to the expectation, only small changes in epidural pressure were observed during the 2 hours period at maximum temperature (41.5-42.5°C); the values remained within 1 SD of the mean at normotemperature. Apparently, brain oedema is not developing in dogs during WBHT treatment at levels up to 42.5°C. However, we did not continue the measurement of cerebral pressure during the cooling phase and afterwards. Therefore it can not be excluded that brain oedema may develop following WBHT. For the future patient treatments it was decided that patients with brain metastasis would be excluded from the clinical study, to avoid the possibility of running into problems by the development of oedema or haemorrhage within the intracranial metastasis.

### Liver

In heat stroke victims, liver centrilobular necrosis is a frequent observation (Marty and Samii 1983).

Pettigrew et al. (1974B) observed liver enzyme abnormalities in patients who

underwent WBHT at temperatures above 41.8°C. This finding could not be confirmed by Mackenzie et al. (1975) who used the same technique (hot wax) and treated all patients at temperatures above 42°C. They observed increased liver enzyme values but these were no limiting factor for the level of hyperthermia. Blair and Levin (1978) report liver damage (in 5 patients) as the major complication following WBHT in a series of 18 patients. This toxicity becomes important at temperature levels above 42°C. The danger of liver damage seems to increase by previous consumption of alcohol or the use of enzyme-inducing drugs such as phenobarbital.

As mentioned in chapter IV an increase of levels of liver enzymes was seen in the dogs with a maximum value at 24 hours. At treatment temperatures of 42°C the increase was 5 to 10 times the starting value. It was concluded that liver toxicity in patients could be avoided by giving WBHT at a maximum temperature of 42°C provided they had normal liver functioning prior to treatment.

#### Blood coagulation

In many heat stroke victims diffuse intravascular coagulation (DIC) was found at post mortem examination (Chao et al. 1981).

Pettigrew et al. (1974B) report on 4 patients dying with DIC within 48 hours of treatment. Three of these patients showed massive tumour necrosis. This suggested a causative relation between tumour regression and DIC, which is supported by another finding of the same group namely that platelets did not decrease in patients who did not show tumour regression (Ludgate et al. 1976). Priesching (1976) observed haemorrhage of tumour twice, resulting in death of the patients. The haemorrhage may have been the effect of either tumour necrosis, DIC or a combination of both.

In our initial experiments with dogs (chapter IV), a decrease in number of platelets with a mean value of 75% was observed, combined with an increase in fibrinogen degradation products (FDP). One dog died due to the occurrence of DIC.

Consequently, monitoring of coagulation parameters was included in the schedule of pre-, durante - and post- WBHT treatment patient care.

#### Decubitus

Priesching (1976) observed decubitus in 6 of his (48) patients. During core temperatures of 42°C, induced in the hyperthermia cabin or by peritoneal perfusion, necrosis very easily develops at sites of pressure, e.g., where infusion systems or ventilation tubes are fixed or at the sacrum of the patient.

This is a consequence of local hypoxia, which renders cells more sensitive for hyperthermia.

Ollendiek (personal communication, 1978) also stressed the importance of avoiding pressure with the installation of the patient.

In the dogs no decubitus was observed. It was decided to avoid the occurrence of pressure sites during the future patient treatments by the use of a special mattress and cushions.

Based on the above mentioned information, the following criteria for patient acceptance were drafted. Age was not considered to be a limiting factor, presuming the general condition of the patient was according to the selection criteria.

The cardiovascular and respiratory systems should be able to meet the demands imposed by WBHT. This was investigated by previous history (no symptoms of myocardial hypoxia), X-ray of the chest and, later in the series, by ergometry (performance up to 120 Watts).

As the liver might be especially sensitive to heat, patients with severe liver abnormalities, revealed either by laboratory tests, or isotope scanning, were excluded.

A brain isotope scan was done in order to exclude patients with brain metastasis, as this carries the risk of a fatal complication due to bleeding or development of oedema in the intracranial tumour.

Coagulation factors should be normal.

The development of decubitus should be prevented by the avoidance of pressure sites during the WBHT treatment procedure.

On the basis of the knowledge described in the chapters II, III and IV and the considerations described above, we designed the clinical study as follows.

1. As the experimental studies indicate that hyperthermia is a very promising modality for the treatment of malignant tumours, it was considered justified to offer the treatment to patients for whom the conventional therapy was judged insufficiently to achieve good -either palliative or curative- results.
2. It had been demonstrated that the Pomp Siemens cabin was suitable for the induction of WBHT.
3. Criteria for patient eligibility had been drafted.

The first step in the approach of the patient always was obtaining informed consent. The patient was told that the WBHT treatment was experimental in terms of unknown toxicity and unknown results, and the procedure of the

pretreatment examination, the treatment itself and the treatment monitoring measures were explained.

Only after acceptance by the patient the procedure was started.

Patients not accepted

Fifty patients for whom WBHT treatment was considered, did not meet all criteria for acceptance. The decision to choose for WBHT was made in three stages which are discussed separately.

Stage I; before the patient was acquainted to the consideration.

In 5 patients the choice was in favour of other antitumour therapy, in 1 patient with disabling pain and a short life expectancy, chordotomy was successful. WBHT was deemed not justified in 2 patients as there was no possibility for combination with a second treatment modality and in 6 patients where combination with local radiotherapy on part of the tumour was possible but in whom the quality of life in the near future was expected to be determined mostly by rapidly progressing metastasis elsewhere. In 4 patients WBHT was not administered as the tumour response would not be evaluable due to tumour size not measurable (n=1), unknown primary tumour (n=1) or a multimodal

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Table V-2 PATIENTS NOT ELIGIBLE FOR WBHT TREATMENT

rectum and colon	n = 7
lung and trachea	n = 8
kidney	n = 6
various sarcomata	n = 7
head and neck	n = 5
bladder and urethra	n = 3
malignant melanoma	n = 3
mesothelioma	n = 2
breast	n = 2
uterine cervix and uterus	n = 2
Hodgkin's disease	n = 2
oesophagus	n = 2
pancreas	n = 1
	_____
	n = 50

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Table V-3 SUMMARY OF PATIENTS ACCEPTED FOR WBHT TREATMENT

Patient sex age	tumour histology	previous therapy	current therapy	no of WBHT sessions
1 F 53	undifferentiated breast ca	S,R,C,H	HT*	2
			HT**+ C (1)	1
2 F 62	breast adeno ca	S,R,C,H	HT	1
			HT + C (1)	1
3 M 30	malignant melanoma	S,C	HT	1
4 M 50	malignant melanoma	S,R,C	HT	3
			HT + R (30)	"
5 M 51	lung adeno ca	none	HT + R (24-49)	3
6 M 42	lung adeno ca	none	HT + R (50)	2
7 M 57	lung squamous cell ca	none	HT + R (46)	2
8 F 54	rectum adeno ca	S,R,C	HT + R (20)	2
9 F 52	breast adeno ca	S,R,C,H	HT	1
			HT + R (18)	"
10 M 44	colon adeno ca	S,R	HT + R (19.5)	2
			HT + C (2)	1
11 M 62	pleural mesothelioma	none	HT + R (19.5)	1
12 M 20	osteosarcoma	S,R,C	HT	1
			HT + R (67)	"
13 F 34	pharyngeal adenocystous ca	R	HT + R (55-65)	1
14 M 35	fibrosarcoma	none	HT + R (60)	1
15 F 39	cervical squamous cell ca	R,C	HT + R (20)	2
16 F 62	colon adeno ca	S,R	HT + C (2)	3
17 M 51	lung adeno ca	none	HT + C (2)	1
18 F 51	sinus adenocystous ca	S,R	HT + R (9)	1
19 M 44	leiomyosarcoma	S	HT** + R (20)	1
20 F 56	colon adeno ca	S	HT + R (64.5) + C (2)	2
21 M 51	pleural mesothelioma	none	HT + R (24)	1
22 M 57	rectum adeno ca	S,R,C	HT + R (15-20)	1
23 M 38	leiomyosarcoma	S	HT + R (60)	2
24 M 56	gastric adeno ca	S	HT + R (20)	1
25 F 65	kidney adeno ca	S,R	HT + R (15-20)	2
26 F 51	kidney adeno ca	S,R,H	HT + R (15)	1
27 M 69	pleural mesothelioma	none	HT + R (2)	1

The used abbreviations in this table are:

F = female; M = male; S = surgery, R( ) = radiotherapy (dose in Gy); C( ) = chemotherapy (1 = melphalan, 25 mg; 2 = 5 fluorouracil, 10 mg/kg body weight); H = hormonal therapy; HT = hyperthermia, \*40.5°C, \*\*41.5°C, remaining sessions 41.8 - 42.0°C.

treatment, administered at the same time (combination of chemotherapy, radiotherapy and misonidazole, n = 2). In 17 patients the previous history gave evidence of insufficient heart- and/or lung function or of liver metastasis. Two patients had been treated previously with vinca-alkaloids, which might render them sensitive to the occurrence of neuropathy following WBHT treatment, as was described by Barlogie et al. (1979).

One patient was considered to be uneligible as he was mentally disabled and not fit to pass informed consent.

Stage II; informed consent.

Four patients refused WBHT as they felt averse to be treated with a non-established therapy.

Stage III; screening.

In 7 patients the screening procedure revealed obstacles. These consisted of insufficiency of heart function (n = 1) or lung function (n = 1), liver metastasis including liver function disturbance (n = 2) or brain metastasis (n = 3). In 1 patient tumour progression caused a spinal cord lesion, which made him unable to undergo the WBHT procedure.

Tumour origins in the group of patients uneligible for WBHT treatment are listed in table V-2.

#### Patients accepted

Twenty-seven patients, 11 female and 16 male, aged 20 - 69 years with a mean of 49.5 years, were accepted for WBHT treatment. These patients, their tumour histologies and a summary of previous history and present therapy, are listed in table V-3. Detailed information on each patient is given in the paragraph "Case reports".

#### The WBHT treatment procedure

The procedure was gradually improved over the patient series, therefore the treatment procedure was not as extensive in the first patient as it was in the last patients.

The procedure as described below is the final result of this development.

Once the patient had passed informed consent and pretreatment examinations, the procedure was planned. One day before WBHT the patient was admitted to the hospital. On this day control X ray photographs of the thorax and an ECG

record were done, zero time blood samples were collected and tumour dimensions were measured. The patient was seen by the anaesthetist and the procedure was, again, discussed with the patient.

On the day of WBHT the following preparatory measures were taken:

- The rectum was emptied by enema to ensure reliable rectal temperature monitoring.
  - The patient was given premedication (papaveretum 0.3 - 0.4 mg/kg body weight and scopolamine 0.004 - 0.006 mg/kg body weight intramuscularly) and prevented from cooling by use of an aluminium foil blanket.
  - Starting with patient 19, following sedation with intravenously administered diazepam (0.1 - 0.2 mg/kg body weight), a 7 French 80 cm long Cordis femoro-renal A2 catheter was inserted into the left femoral vein in the groin and advanced, under X-ray control, until its tip was positioned in one of the hepatic veins.
  - The patient was placed on a water mattress kept at a temperature of 44-46°C (using a Churchill Thermocirculator LTSM thermostatically controlled heater circulator). The water mattress rested on an antidecubitus mattress filled with polystyrene grains.
  - ECG monitoring electrodes were fixed on the thoracic wall.
  - An intra-arterial catheter was introduced into the radial artery and advanced into the brachial artery, a 7 French gauge KMA thermodilution Swan Ganz catheter via the left subclavian vein into the pulmonary artery and an intravenous catheter into one of the fore arm veins. The fluids administered intravenously were heated to a temperature of 42°C following passage through a heat-exchanger (Treonic H150 haemoheater model 114).
  - Anaesthesia was induced with methohexitone; the patient was paralysed, intubated with a cuffed endotracheal tube and ventilated using a Siemens Elema servo-ventilator 900A. Anaesthesia was maintained with an N<sub>2</sub>O/O<sub>2</sub> (66%/33%) mixture, humidified and warmed to 40-42°C. This was supplemented with fluothane or enflurane in some patients.
- Rectal, oesophageal, nasopharyngeal, intramuscular and subcutaneous thermocouple probes were placed; probes were also placed between the skin and the water mattress, against the tympanic membrane and, where possible, in the tumour. For safety reasons an additional, independent, thermistor, part of the Hewlett-Packard compact monitor, was placed in the oesophagus.
- A bladder catheter was introduced to enable monitoring of urine output during hyperthermia.



- In some patients it was possible to place one or more pH electrodes (Philips C902S tissue pH electrode) into the tumour, using the method described by van den Berg et al. (1982). Following sterilization in Cidex solution (Johnson and Johnson, Benelux B.V.), the electrode was calibrated in sterile NBS buffers at pH = 6.841 and 7.385. To allow the introduction of the (fragile) electrode into tissue, a small incision in the skin, mucosa or tumour surface was made. The pH was measured with a Knick pH-meter (model 645; input impedance  $2.10^{12} \Omega$ ) in conjunction with a chart recorder.
- Special cushions filled with polystyrene grains were placed at pressure sites to protect against decubitus. Pressure points arising between monitoring lines and skin were avoided by folded gauzes if indicated.
- Finally, the patient was wrapped in plastic film.

Heating was started by closing the hood of the cabin and raising the air temperature in the cabin to 60-65°C. The circulating water in the mattress was kept at a temperature of 44-46°C. When the intraoesophageal temperature reached 41°C the temperature of the air and of the water in the mattress was

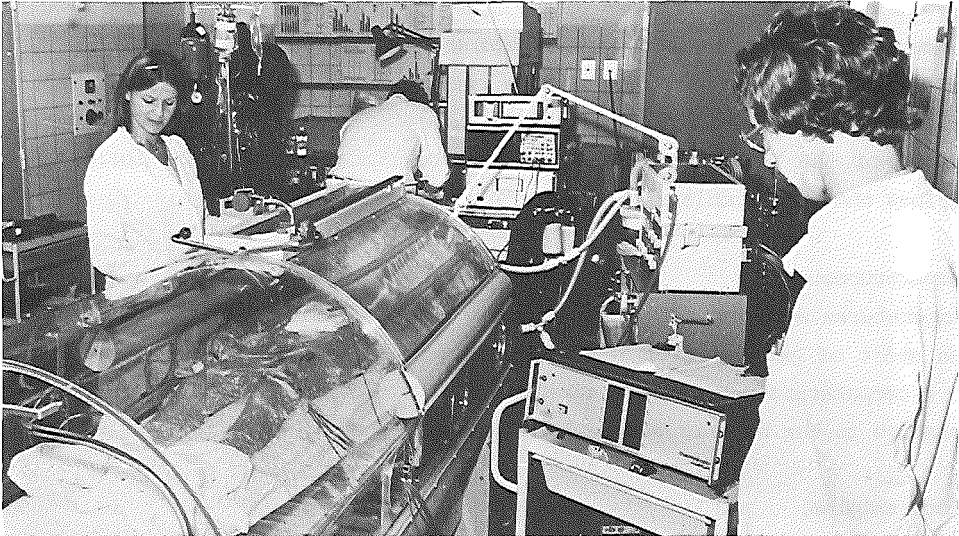


Fig. V - 1 THE ADAPTED POMP SIEMENS CABIN METHOD

This photograph shows the application of a WBHT treatment. The patient lies in the cabin on a warm water mattress, surrounded by warm air and wrapped in plastic foil, with the head outside. At the background the anaesthesia and physiology monitoring equipment is visible; left in the front the thermometry monitoring equipment.

decreased to about 36°C. The patient's core temperature was maintained at 41.8-42°C for 2 hours (plateau phase) by adjusting the air and water temperature. The clinical set up of the WBHT treatment is presented in figure V-1. The various phases during a WBHT session, i.e. "heating", "plateau phase" and "cooling" are indicated in figure V-2.

Cooling at the end of treatment was achieved by a combination of opening the cabin, removing the plastic foil, blowing cool air over the unwrapped patient and circulating cold water through the mattress.

When the intraoesophageal temperature had decreased below 40°C, the anaesthesia was terminated and the patient regained consciousness. Following WBHT the patient was transferred to the intensive care unit, where monitoring of pulmonary artery and wedge pressure, cardiac output and arterial pressure was continued.

If no complications arose, the patient was transmitted to a standard hospital room on the next day and dismissed from the hospital 2-3 days following treatment.

#### Monitoring procedures

Monitoring of particularly cardiovascular and physiological parameters during WBHT treatment became gradually more extensive throughout the study. After a patient (no. 18) had died due to hepatic necrosis following WBHT, monitoring in one of the hepatic veins became part of the procedure. The following describes the final monitoring procedure:

##### Temperatures.

Temperatures were monitored continuously and registered every 10 minutes, from the start of heating till 30-60 minutes after the start of cooling, when the core temperature had decreased below 40°C. During only one treatment the temperature in the hepatic vein was also measured.

##### Blood samples.

Arterial, venous, mixed venous and hepatic venous blood samples were taken at various "marker" times before, during and after WBHT treatments, as far as the respective compartments were accessible (Faithfull 1983). These marker times were

- 1) before induction of anaesthesia, 2) at the start of heating, 3) when the plateau temperature of 41.8°C was reached, 4) after 1 hour at plateau,

5) at the end of plateau and 6), 7) and 8) 15, 30 and 45 minutes, respectively, following the start of cooling. Marker times 2 - 7 are indicated in figure V-2. Laboratory analysis included blood gases, electrolytes, haematology and biochemical parameters.

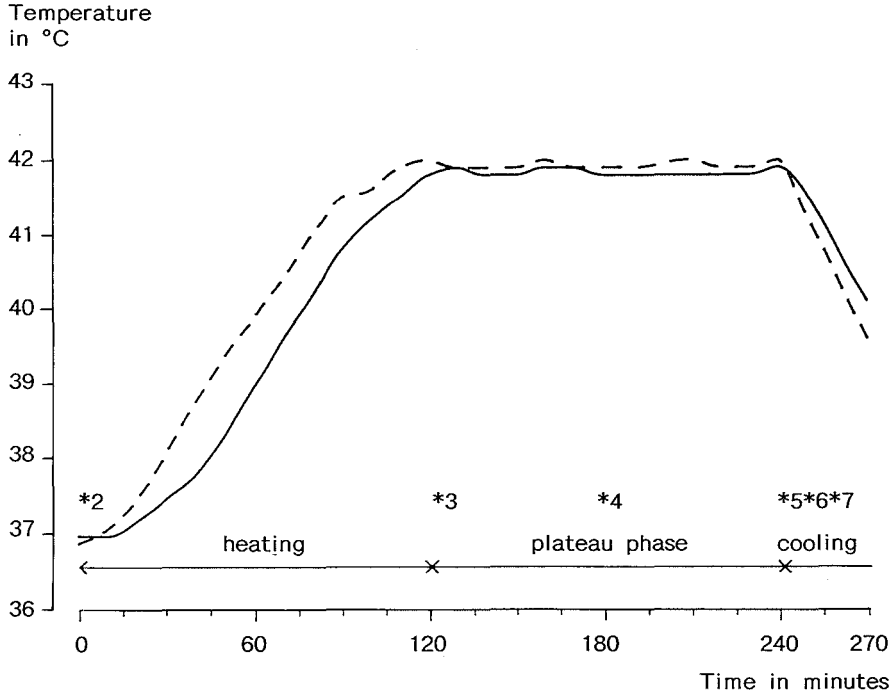


Fig. V - 2 COURSE OF TEMPERATURE DURING A WBHT SESSION

Course of rectal and oesophageal temperatures during WBHT in patient no. 13: — rectal and --- oesophageal temperature.

\* (2 - 7): marker times; the points of time where blood samples were taken for analysis of blood gases, electrolytes, haematological and biochemical parameters.

#### Cardiovascular system.

Every 10-15 minutes the following parameters were recorded: heart rate, systolic, diastolic and mean arterial and pulmonary artery pressures, cardiac output, pulmonary capillary wedge pressure and central venous pressure (Faithfull 1983).

Respiration.

Measurements were taken of expired carbon dioxide percentage which was maintained between 3 and 4% by adjusting the tidal volume, and of carbon dioxide minute production (Faithfull 1983).

Urinary production.

Urinary production was measured and collected from 24 hours before the start of heating, when the patient was hospitalized. At the day of WBHT, urine was collected in 2 hour portions from the start of heating till 12 hours afterwards. Analysis of electrolyte concentrations in the urine was performed.

pH.

When possible, intratumour pH was measured, beginning after the induction of anaesthesia. Besides, several subcutaneous pH measurements were performed. Because the time required to reach equilibrium following insertion of the electrode was found to be in the order of 30-90 minutes, the values obtained during the heating phase were considered unreliable (Wike-Hooley et al. 1985). Measurements were recorded continuously.

#### Hepatic clearance of ICG

Hepatic damage was a frequently observed complication following WBHT, as evident from increases in serum transaminase (SGOT). This was previously reported by other investigators ((Pettigrew et al. 1974A, Mackenzie et al. 1975), and observed by us in the first series of experiments with dogs and during the clinical study in many patients. In one patient liver damage even ended fatally. The impression was that disturbed tissue oxygenation might have played a role. For this reason it was decided to attempt measurement of hepatic blood flow (HBF) during hyperthermia. The continuous infusion technique introduced by Bradley et al. (1945) is a universally accepted one for the measurement of HBF on the basis of the Fick principle (the volume of blood passing through an organ is equivalent to the ratio of the amount of "marker" taken up by the organ and the difference between arterial and venous concentration of the "marker"). These investigators used bromsulphalein (BSP), but indocyanine green (ICG) is now more commonly used, as this dye (under normothermic conditions) has been shown to have no extrahepatic extraction routes (Cherrick et al. 1960; Caesar et al. 1961), which does not hold for BSP. The use of a hepatic vein catheter enables the measurement of concentration decrease

of ICG over the liver, and on the basis of certain assumptions HBF can be calculated from this.

#### Hepatic function tests.

The hepatic clearance of ICG was determined on four occasions in patients nos. 20, 21 and 22 while undergoing WBHT. The patients all had normal liver function as determined by routine laboratory tests and HIDA (isotopic liver function test). Following introduction of a catheter into one of the hepatic veins, a 15 mg "loading" dose of ICG was administered and this was followed by continuous intravenous infusion at the rate of 0.167 or 0.333 mg.min<sup>-1</sup>. The infusion rate was controlled by use of a Hospal KIO infusion pump.

After allowing at least 20 min for equilibration, paired blood samples were withdrawn simultaneously from the hepatic vein and brachial artery at various times during the treatment (preinduction, start of heating, start of plateau phase, midplateau, and 15 min after initiation of cooling) for ICG and oxygen determinations. Infusion of ICG was continued until 15 min after termination of WBHT, giving a mean total infusion time of 350 min (range 320-375). Thereafter, blood samples were taken every 2 hr to enable investigation of plasma disappearance of ICG following treatment. The total dose of ICG administered never exceeded 2 mg.kg<sup>-1</sup> body weight.

ICG was prepared for intravenous infusion by dissolving the dye in sterile solvent to a concentration of 5 mg.ml<sup>-1</sup>. The dye was stabilized by the addition of albumin to give a concentration of 1.8% albumin.

Blood samples were collected in heparinized syringes. Due to the slow infusion rate of dye (necessary for such long infusion periods), determination of ICG was done on undiluted plasma. As the blank density appeared to change during a treatment session (which usually lasted several hours), a blank correction according to the principle introduced by Gaebler (1945), and as adapted by Winkler and Tygstrup (1960), was applied. Dye concentration was thus calculated as:

$$c = \frac{D_{805} - f \times D_{600}}{E_{805} - f \times E_{600}}$$

where D is the optical density at 805 and 600 nm respectively, E is the extinction coefficient of ICG in plasma at the same wavelengths and f is the blank factor, i.e., plasma blank at 805 nm or plasma blank at 600 nm.

Dye determinations were performed in a Carl Zeiss PMQ11 spectrophotometer.

#### Calculations

a) Hepatic blood flows were calculated by the Fick principle, according to the method of Bradley et al. (1945), where

$$\text{EHBFB} = \frac{\text{removal rate}}{(C_A - C_{HV})} \times \frac{1}{1-Ht}$$

where EHBFB = estimated hepatic blood flow

removal rate = infusion rate of ICG (under steady state)

$C_A$  = arterial dye concentration

$C_{HV}$  = hepatic venous dye concentration

Ht = Haematocrit.

$1/1-Ht$  is a correction for red blood cell volume

b) Hepatic extraction ratios (E) were calculated from

$$E = \frac{C_A - C_{HV}}{C_A} \quad (\text{Huet et al. 1981})$$

c) Clearance ( $l \cdot \text{min}^{-1}$  cleared by the liver) is derived from the product of the extraction and the liver blood flow (Fick principle)

$$Cl = \text{EHBFB} \times E \quad (\text{Huet et al. 1981})$$

d) Half-life ( $t_{1/2}$ )

This was calculated from the formula:

$$t_{1/2} = \frac{0.6931 \times \text{vol. of distribution}}{Cl} \quad (\text{Huet et al. 1981})$$

The volume of distribution is the plasma volume. This was derived from the body weight ( $\text{ml} \cdot \text{kg}^{-1}$ , dependent on age and sex, from Documenta Geigy, 1976, p. 551) and the haematocrit.

#### Evaluation of tumour response

##### - Palpable tumours

Tumour dimensions were measured at regular times with callipers in two or

three directions. In patients with multiple superficial tumour lesions, a selection of at most 10 nodules was made. From the dimensions measured the tumour surface area or volume was calculated.

- Non palpable tumours

In lung tumours, tumour dimensions visible on anteroposterior and latero-lateral X-ray photographs were measured and the volume was calculated. Intra-abdominal tumour dimensions were calculated on the base of CT scanning. In two patients (no. 19 and 24), the situation before and after WBHT was judged during laparotomy. In three patients (no. 9, 18 and 27, who died 1, 3 and 1 week(s), respectively, following WBHT), the tumour reaction was investigated histologically post mortem.

Tumour response was determined using WHO criteria (Miller 1981). Abbreviated, this encompassed the following response levels:

progression: 25% or more increase in tumour;

NC : "no change" : less than 25% increase and less than 50% decrease in tumour volume;

PR : "partial response" : at least 50% decrease in tumour volume;

CR : "complete response" : disappearance of the tumour; both partial and complete regression had to be maintained for at least one month.

Tumour dimensions were measured before the start of the treatment (series) and at intervals of 1 week to 2 months after the end of the treatment.

Case reports

In a period of 3½ years 27 patients received 45 whole body hyperthermia treatments. In this paragraph a report will be given on each of the patients. These case reports will be restricted to a description of the patient, his previous history and pre-treatment status, the kind of treatment given, the response to the treatment (objective and subjective), and the specific toxicity, if any, as a consequence of WBHT.

During this 3½ year period, the method of WBHT induction, the level of pre-treatment screening considered to be necessary, and the policy with regard to the combination of WBHT with other treatment modalities, i.e. treatment scheduling, were gradually changed on the basis of acquired experience. These matters will be discussed in other chapters.

### CASE 1

A 53-year-old female, with a 20-month-history of breast carcinoma, locally progressive despite extensive previous therapy.

Histopathology: undifferentiated carcinoma.

Previous therapy: surgery; radiotherapy of both regional and various distant metastases; hormonal therapy (megestrol, nolvadex, lynoral) and chemotherapy (combination endoxan, methotrexate and 5 FU, combination adriamycin and vincristin, topically applied 5 FU).

Pretreatment status: extensive tumour involvement of the homolateral thoracic wall, surrounded by a zone of cutaneous lymphangitis carcinomatosa. Distant metastasis not demonstrated.

Current treatment: 3 whole body hyperthermia (WBHT) treatments with time intervals of 1 and 2 weeks respectively with additional 433 MHz local hyperthermia of the thoracic wall.

WBHT 1 : Maximum rectal temperature (T rect.max.) 40.4°C;  
plateau 140 minutes at 40.1°C;  
maximum tumour temperature (T tum.max.) 43.8°C.

WBHT 2 : T rect.max. 41.4°C; plateau 150 minutes at 41.2°C; T tum.max. 43.8°C.

WBHT 3 : T rect.max. 41.6°C; plateau 210 minutes at 41.4°C; T tum.max. 47°C,  
combined with melphalan 25 mg given at T rect. 41°C.

Toxicity: no special problems following first two treatments. During the third treatment a severe third-degree burn of the thoracic wall developed, diameter 10 cm and including ribs. This probably resulted from standing wave formation in the microwave field causing an unobserved hot spot.

Objective tumour response: the tumour was progressive following hyperthermia only. Following the combination hyperthermia and melphalan, the tumour did not progress for 3 months.

Palliation: none

The patient died 12 months following the first hyperthermic treatment, due to local tumour progression.

### CASE 2

A 62-year-old female, who had undergone breast amputation 17 years previously, and in whom the tumour recurred locally 20 months ago.

Histopathology: poorly differentiated adenocarcinoma.

Previous therapy: surgery; radiotherapy of the thoracic wall and the sternum; chemotherapy (combination of endoxan, methotrexate, 5 FU) and hormonal therapy



(niagestin).

Pretreatment status: intracutaneous and subcutaneous tumour infiltration around the scar, extending in depth around the sternum and to the hetero-lateral breast. Midsternal a large subcutaneous nodule was present. Liver-scan by <sup>99</sup>Techetium (<sup>99</sup>Tc): suspect for metastasis; no increased serum levels of liver enzymes.

Current therapy: 2 WBHT treatments with a time interval of 3½ weeks were given, the second in combination with melphalan.

WBHT 1 : T rect.max. 41.9°C; plateau 2 hours at 41.8°C;

WBHT 2 : T rect.max. 41.8°C; plateau 2 hours at 41.7°C;

melphalan 25 mg was administered at T rect. 41°C.

Toxicity: following first treatment, small third degree burns of both great toes occurred, which however caused no trouble to the patient.

Objective tumour response: following the first treatment the subcutaneous nodule rapidly regressed to 44%, but started growing again 3 weeks later, thus, following WHO criteria, only "no change" was achieved. Following the second treatment "no change" was observed, for a duration of 2 months.

Palliation: a 2-month relief of pain and dyspnea following the first treatment. The patient died 9 months after the first hyperthermia treatment due to local tumour progression.

### CASE 3

A 30-year-old male, with a 5 years history of malignant melanoma, metastatized.

Previous therapy: surgery; chemotherapy (DTIC and BCG).

Pretreatment status: multiple intracutaneous and subcutaneous metastases, enlarged liver, palpable 4 cm below lowest rib during normal inspiration, probably due to tumour involvement; no increased serum levels of liver enzymes.

Current therapy: 1 WBHT treatment. T rect.max. 41.8°C; plateau 2 hours at 41.8°C;

Toxicity: at the end of the cooling phase ventricular tachycardia suddenly developed. Blood chemistry revealed acidosis and electrolyte changes (a decrease in Ca and K). Following administration of NaHCO<sub>3</sub>, sinus nodal rhythm slowly returned.

On the day following hyperthermia it became clear that all toes had incurred burns, with third degree burns of the first two toes of both feet. This could have been caused by poor circulation in the feet of this very tall patient.

These burns rendered the patient unable to walk.

Objective tumour response: up to 20% regression of cutaneous metastases during the first 3 weeks, followed by regrowth, which thus means "no change".

Palliation: not applicable, as the patient did not suffer pain previously. This patient died 3 months after WBHT treatment.

#### CASE 4

A 50-year-old male, in whom excision of enlarged neck nodes of malignant melanoma had been performed 6 months previously. Primary tumour unknown.

Histopathology: malignant melanoma.

Previous therapy: surgery; radiotherapy, interrupted when hematogenous metastasis appeared; chemotherapy (DTIC, C parvum, MeCCNU).

Pretreatment status: multiple neck nodes, multiple cutaneous and subcutaneous metastases, enlarged liver. Serum levels of liver enzymes were within the normal range.

Current therapy: 3 WBHT treatments with time intervals of 1 week, were given within a series of radiotherapy (6 x 5 Gy in 3 weeks) of the supraclavicular lymph nodes.

WBHT 1: T rect.max.  $41.8^{\circ}\text{C}$ , plateau 2 hours at  $41.7^{\circ}\text{C}$ ;

WBHT 2: T rect.max.  $41.7^{\circ}\text{C}$ , plateau 2 hours at  $41.7^{\circ}\text{C}$ ;

WBHT 3: Details on the temperature data were lost but the treatment was recorded to have been 2 hours at  $41.8^{\circ}\text{C}$ .

Toxicity: following the first treatment, the patient was admitted to the Intensive Care Unit in a delirious state. This was ascribed to toxicity of atropin, which had been administered in high doses during WBHT. In this patient, the heating rate was relatively low ( $1.4^{\circ}\text{C/hr}$ ), which was probably related to the excessive sweating observed. High dosages of atropin were given to decrease the sweating. The mental status returned to normal during the night following WBHT. Several second-degree burns were observed. These were located at sites where the skin had been directly exposed to currents of warm air from the electrical heaters beneath the patient.

Objective tumour response: of the lymph nodes treated in combination with radiotherapy, the previously irradiated group showed "no change", while the previously non irradiated group showed "partial response". The overall response in these lymph nodes was therefore recorded as "no change". The tumour metastases treated with hyperthermia only also showed no change. The patient was lost to follow-up after two months.

Palliation: not applicable.

The patient was reported to have died 3 months later.

#### CASE 5

A 51-year-old male, in whom a lung carcinoma had been demonstrated 3 months previously.

Histopathology: bronchial adenocarcinoma.

Previous therapy: none.

Pretreatment status: central bronchial tumour, involvement of mediastinal and homolateral supraclavicular lymph nodes.

Current therapy: 3 WBHT treatments with time intervals of 1 week, within a series of radiotherapy (12 x 2 Gy in 3 weeks).

WBHT 1: T rect.max. 41.9°C; plateau 2 hours at 41.7°C;

WBHT 2: T rect.max. 41.9°C; plateau 2 hours at 41.8°C;

WBHT 3: T rect.max. 41.9°C; plateau 2 hours at 41.9°C.

Toxicity: following the first WBHT the patient developed fever and chills with cardiac decompensation and hypotension. The fever diminished spontaneously, the circulatory problems disappeared following administration of lasix. Following the third WBHT the patient showed clinical signs of lung emboli at the tumour site, although the lung scan performed on the third day following WBHT revealed no abnormalities.

Objective tumour response: all known tumour deposits regressed completely within 6 weeks. After this period, various lymph node metastases became apparent in the heterolateral supraclavicular region. The patient received an additional series of radiotherapy: 8 and 9 fractions of 2.5 Gy on the mediastinal and homolateral lymph nodes respectively and 20 x 2.5 Gy on the heterolateral lymph nodes. The heterolateral lymph nodes showed a "partial response" lasting for 6 months, after which progression occurred. The tumour treated with the combined therapy was still controlled 10 months later, when the patient died due to progressing brain metastasis, which had become apparent 6 months following the first WBHT.

Palliation: not applicable.

#### CASE 6

A 42-year-old male, with a 1-month-history of bronchial carcinoma.

Histopathology: bronchial adenocarcinoma.

Previous therapy: none.

Pretreatment status: primary tumour in the apical region of the lung and homolateral mediastinal lymph nodes. The liver  $^{99}\text{Tc}$  scan showed a large liver with heterogeneous uptake; a biopsy showed no abnormalities, laboratory values of liver enzymes were within the normal range.

Current therapy: 2 WBHT treatments with a time interval of 6 weeks, each within a series of radiotherapy (10 x 2.5 Gy in 2 weeks each) of the visible tumour.

WBHT 1: T rect.max.  $42.0^{\circ}\text{C}$ ; plateau 2 hours at  $41.9^{\circ}\text{C}$ ;

WBHT 2: T rect.max.  $41.9^{\circ}\text{C}$ ; plateau 2 hours at  $41.8^{\circ}\text{C}$ .

Toxicity: none.

Objective tumour response: post-treatment X rays of the thorax, showed disappearance of the tumour; no abnormalities except fibrosis resulting from irradiation. The patient was free of disease for 9 months; he then developed brain metastasis. The patient was lost to follow-up 11 months after the first WBHT treatment, at which point he returned to his native country, Turkey. However, notification of death was received 28 months after the first WBHT treatment.

Palliation: not applicable.

#### CASE 7

A 58-year-old male, with a 2-month-history of bronchial carcinoma.

Histopathology: moderately well differentiated squamous cell carcinoma.

Previous therapy: none.

Pretreatment status: tumour in the median lobe of the lung infiltrating in the main bronchus. The liver was enlarged and tender, spontaneously and at palpation but the liver  $^{99}\text{Tc}$  scan showed no abnormalities and serum levels of liver enzymes were within the normal range. X-ray photographs of the heterolateral lung showed a round shadow suspicious for metastasis.

Current therapy: the patient received 2 WBHT treatment with a time interval of 5 weeks, each treatment within a series of radiotherapy (13 and 10 x 2 Gy respectively), of the macroscopic tumour and the mediastinum.

WBHT 1: T rect.max.  $42.1^{\circ}\text{C}$ ; plateau 2 hours at  $41.9^{\circ}\text{C}$ ;

WBHT 2: T rect.max.  $41.8^{\circ}\text{C}$ ; plateau 2 hours at  $41.8^{\circ}\text{C}$ .

Toxicity: no special problems.

Objective tumour response: the tumour regressed partially; regrowth occurred after 1 year.

Palliation: the pain in the hepatic region disappeared for 3 weeks.

The patient died 22 months after the first WBHT treatment due to tumour progression in both lungs.

#### CASE 8

A 54-year-old female, with an 18-month-history of rectum carcinoma, locally recurring despite extensive previous therapy.

Histopathology: rectal adenocarcinoma.

Previous therapy: surgery of the primary tumour and of recurrent tumour 5 months later, with construction of a preternatural anus; chemotherapy (5 FU and CCNU); radiotherapy.

Pretreatment status: large recurrent tumour, fixed to the sacrum and the left pelvic bone with infiltration through the uterine and vaginal walls. This tumour was the cause of much pain, not controllable with morphine analgesics. No signs of distant metastasis.

Current therapy: the patient received 2 WBHT treatments with a time interval of 1 week, within a series of radiotherapy, 10 x 2 Gy in 2 weeks.

WBHT 1: T vagina max. 41.8°C; plateau 2 hours at 41.7°C;

WBHT 2: T vagina max. 41.8°C; plateau 2 hours at 41.7°C.

Toxicity: no special problems.

Objective tumour response: loss of a considerable amount of necrotic material via the pre-existing vaginal fistula; the tumour showed a rapid partial regression, but progression started 6 weeks later.

Palliation: the pain had disappeared completely at the moment that the patient regained consciousness following the first WBHT treatment. This improvement lasted for only 3 weeks.

The patient died 8 months following WBHT due to local tumour progression.

#### CASE 9

A 52-year-old female, with a 45-month-history of breast carcinoma, metastatized.

Histopathology: highly infiltrating adenocarcinoma.

Previous therapy: surgery of the primary tumour; radiotherapy of the recurring tumour and of various bone metastasis; hormonal therapy (ovariectomy, niagestin, nolvadex) and chemotherapy (combination of endoxan, methotrexate and 5 FU, combination of adriamycin and vincristin).

Pretreatment status: large metastatic tumour in the pelvis, fixed to the pelvic bone wall with infiltration of the bladder, the vaginal wall and the uterine cervix. X ray photograph of the lungs suspect for carcinomatous lymphangitis. The pelvic tumour caused considerable pain.

Current therapy: the patient received 1 WBHT treatment, T rect.max.  $42.1^{\circ}\text{C}$ ; plateau 2 hours at  $41.9^{\circ}\text{C}$ , within a series of radiotherapy, 9 x 2 Gy in 2 weeks on the pelvic tumour.

Toxicity: following WBHT the patient was dyspnoeic and was respirated artificially for 1 night. The dyspnoea was due to fluid accumulation in the lungs. The patient recovered slowly; two weeks after WBHT chemotherapy was started (combination of prednison, vincristin, endoxan and 5 FU) but 1 week later the patient died.

Objective tumour response: at autopsy the previously large tumour in the pelvis had regressed completely and was macroscopically undetectable. Carcinomatous lymphangitis of the lungs was evident and there was abundant pleural effusion.

Palliation: the pelvic pain disappeared immediately following WBHT and did not return during the 3 weeks that the patient was alive.

#### CASE 10

A 44-year-old male, with an 8-year-history of colon carcinoma, locally recurring.

Histopathology: adenocarcinoma.

Previous therapy: surgery of the primary tumour and 7 years later radiotherapy of recurrent tumour.

Pretreatment status: a large tumour in the abdomen, ulcerating through the abdominal wall, causing considerable pain. No signs of distant metastasis.

Current therapy: the patient received 3 WBHT treatments, with time intervals of 2 and 10 weeks respectively. The first 2 WBHT treatments were given within a series of radiotherapy, 13 x 1.5 Gy; the third treatment was given in conjunction with a course of 5 FU injections, the first of which was given during WBHT, at the moment that a rectal temperature of  $41.0^{\circ}\text{C}$  was reached.

WBHT 1: T rect.max.  $42.3^{\circ}\text{C}$ ; plateau 2 hours at  $42.1^{\circ}\text{C}$ ;

WBHT 2: T rect.max.  $42.1^{\circ}\text{C}$ ; plateau 2 hours at  $41.9^{\circ}\text{C}$ ;

WBHT 3: T rect.max.  $41.8^{\circ}\text{C}$ ; plateau 2 hours at  $41.8^{\circ}\text{C}$ .

Toxicity: no special problems.

Objective tumour response: following WBHT combined with radiotherapy, the tu-

mour showed a "partial response" lasting for 3 months. Following WBHT combined with 5 FU, there was "no change" for a duration of 6 months.

Palliation: following the first WBHT, the pain disappeared for a period of 2 months. There was no palliative effect following the third WBHT.

The patient died 11 months following the first WBHT due to local tumour progression.

#### CASE 11

A 55-year-old male with a 2-month-history of malignant pleural effusion.

Histopathology: resembling malignant mesothelioma.

Previous therapy: none but a palliative draining of pleural fluid.

Pretreatment status: pleural tumour nodules at various sites which were demonstrated by thoracoscopy. There were no indications for distant metastases.

Current therapy: the patient was treated with 1 WBHT treatment, T rect.max. 42.1°C, plateau 2 hours at 41.9°C, within a series of radiotherapy, 13 x 1.5 Gy in 2 weeks.

Toxicity: following WBHT, the patient developed atrial fibrillation, for which he was digitalized.

Objective tumour response: the tumour was not measurable on X-ray photographs, but pleural effusions did not recur during the rest of the patient's life; he was disease-free for 21 months, after which period subcutaneous tumour nodules occurred in the homolateral thoracic wall, followed six months later by the occurrence of lung metastasis.

Palliation: not applicable.

The patient died 31 months following WBHT due to progression of metastasis in the thoracic wall and both lungs.

#### CASE 12

A 20-year-old male, with a 5-month-history of a bone tumour of the femur with lung metastasis.

Histopathology: osteosarcoma.

Previous therapy: radiotherapy of the primary tumour, chemotherapy (methotrexate and cis-Platinum). The basal part of 1 lung was irradiated with a total dose of 49 Gy up to 1 week before WBHT.

Pretreatment status: multiple lung metastases. The <sup>99</sup>Tc liver scan showed an enlarged liver with inhomogeneous activity but the serum levels of liver

enzymes were within normal ranges; the  $^{99}\text{Tc}$  brain scan gave dubious result but no clear indication for metastasis.

Current treatment: the patient received 1 WBHT treatment, T rect.max.  $42.0^{\circ}\text{C}$ ; plateau 2 hours at  $41.8^{\circ}\text{C}$ , within a series of radiotherapy, 6 x 1.5 Gy, on the previously irradiated metastases.

Toxicity: no special problems.

Objective tumour response: the irradiated metastases showed a less than partial regression ("no change"); the remainder of the tumour showed no progression during 6 weeks, after which time rapid progression occurred.

Palliation: not applicable.

The patient died 10 weeks after WBHT due to progression of lung metastasis.

### CASE 13

A 33-year-old female presenting a tumour initiating from the parapharyngeal space; complaints of trismus for 12 months, known with malignant tumour including lung metastasis for 4 months.

Histopathology: adenocystic carcinoma.

Previous therapy: recent radiotherapy of the pharynx (40 Gy), of both lungs (22.5 Gy) with boosters on the visible lung metastases (additional 18 Gy), combined with misonidazole (total dose 10.1 g).

Pretreatment status: primary tumour and lung metastases in regression.

Current therapy: the patient received 1 WBHT treatment, T rect.max.  $41.9^{\circ}\text{C}$ ; plateau 2 hours at  $41.8^{\circ}\text{C}$ , within a series of radiotherapy (10 x 2.5 Gy of the pharynx and 5 x 3 Gy for the lung metastasis).

Toxicity: no special problems.

Objective tumour response: complete disappearance of the primary tumour and the lung metastases; 44 months after WBHT a new lung metastasis occurred which was treated by radiotherapy.

Palliation: not applicable.

The patient is alive with presently no evidence of disease, 6 years after WBHT.

### CASE 14

A 35-year-old male with a tumour in the sacroiliacal joint; he had been suffering pain for 9 months, the tumour had been discovered only 2 months prior to referral to our unit.



Histopathology: fibrosarcoma.

Previous therapy: none.

Pretreatment status: a large osteolytic process in the sacroiliacal joint, which caused severe pain and restrictions in mobility. There were no indications for distant metastasis.

Current treatment: The patient received 1 WBHT treatment, T rect.max.  $41.9^{\circ}\text{C}$ , plateau 2 hours at  $41.8^{\circ}\text{C}$ , within a series of radiotherapy, 30 x 2 Gy in 6 weeks.

Toxicity: severe liver damage was observed following WBHT with maximum SGOT and SGPT values of 1328 and 1900 U/l respectively and the patient developed icterus. The SGOT and SGPT values decreased from 1 week after WBHT and were normal 2 weeks after WBHT. As a result of this toxicity it was decided not to proceed with the 2 additional WBHT treatments that had been planned.

Objective tumour response: at the moment that only 20 Gy and one WBHT treatment had been given, the tumour had already regressed by 50%.

Palliation: the pain disappeared immediately following WBHT and the patient could once more use his leg as well as before his complaints started.

2½ months after WBHT had been given, the tumour once more started to grow from the margins of the radiotherapy field, and multiple lung metastases became visible. The patient died 4 months following WBHT.

#### CASE 15

A 39-year-old female with a 20-month-history of tumour of the uterine cervix, which had locally recurred.

Histopathology: poorly differentiated squamous cell carcinoma.

Previous therapy: radiotherapy of the primary tumour, chemotherapy for recurrent tumour (a combination of bleomycin, mitomycin-C and cisPlatinum).

Pretreatment status: a large tumour in the pelvis, causing the abdominal wall to protrude, and which caused moderate pain. There was no evidence for distant metastases, although there were some abnormalities on the liver  $^{99}\text{Tc}$  scans.

Current therapy: the patient received 2 WBHT treatments with a time interval of 1 week, within a series of radiotherapy, 10 x 2 Gy in two weeks.

WBHT 1: T rect.max.  $42.0^{\circ}\text{C}$ ; plateau 2 hours at  $41.9^{\circ}\text{C}$ ;

WBHT 2: T rect.max.  $42.0^{\circ}\text{C}$ ; plateau 2 hours at  $42.0^{\circ}\text{C}$ .

Toxicity: no special problems.

Objective tumour response: the tumour regressed by less than 50% ("no change"), and progression was observed after 2 months.

Palliation: the pain became less severe but did not disappear.

The patient died 4 months following WBHT due to local tumour progression.

#### CASE 16

A 62-year-old female with a 2-year-history of malignant disease of the colon, which had locally recurred.

Histopathology: mucous producing adenocarcinoma.

Previous therapy: surgery of the primary tumour. The patient had received a full course of radiotherapy for a squamous cell carcinoma of the uterine cervix 27 years previously, which made further radiotherapy impossible.

Pretreatment status: a local recurrence with a diameter of 8 cm; the liver was enlarged but  $^{99}\text{Tc}$  scanning revealed no metastases. There were no signs of metastasis elsewhere. The tumour caused severe pain.

Current therapy: the patient received 3 WBHT treatments with time intervals of 2 weeks. Each of the WBHTs was combined with 5 FU, 10 mg per kg bodyweight, administered at the time that rectal temperature reached  $41^{\circ}\text{C}$ . The administration of 5 FU was continued by weekly injections following the third WBHT.

WBHT 1: T rect.max.  $41.9^{\circ}\text{C}$ ; plateau 2 hours at  $41.8^{\circ}\text{C}$ ;

WBHT 2: Details on the temperature data were lost but the treatment was recorded to have been 2 hours at  $41.8^{\circ}\text{C}$ ;

WBHT 3: T rect.max.  $41.9^{\circ}\text{C}$ ; plateau 3 hours at  $41.8^{\circ}\text{C}$ .

Toxicity: no special problems.

Objective tumour response: there was a partial regression lasting 2 months.

Palliation: none.

The patient died 10 months after the first WBHT due to local tumour progression.

#### CASE 17

A 57-year-old male presented with a malignant tumour of the bronchus, diagnosed 2 weeks previously.

Histopathology: poorly differentiated bronchial adenocarcinoma.

Previous therapy: none.

Pretreatment status: a peripheral bronchial carcinoma with supraclavicular and mediastinal lymph node metastases on the homolateral side. Liver  $^{99}\text{Tc}$  and bone  $^{99}\text{Tc}$  scanning revealed abnormalities which may have been indicative of metastases, serum levels of liver enzymes were within the normal range.

Current treatment: the patient received 1 WBHT treatment , T rect.max. 42.2°C; plateau 2 hours at 41.8°C, combined with 5 FU administered when the rectal temperature reached 41°C. Radiotherapy was not considered because of the spreading of the tumour.

Toxicity: in the immediate post-WBHT period there were ventilation problems, which were resolved by the administration of oxygen.

Objective tumour response: the previously rapidly progressing tumour showed some regression but started growing again 1 month later.

Palliation: not applicable.

The patient died 2 months following WBHT due to local tumour progression.

#### CASE 18

A 51-year-old female, with a 45-month-history of tumour initiating from the maxillary sinus.

Histopathology: adenocystic carcinoma.

Previous therapy: radiotherapy and surgery of the primary tumour.

Pretreatment status: multiple lung metastases. The <sup>99</sup>Tc liver scan demonstrated a space occupying process in the hilar region. A functional scintigram of the hepatobiliary system (HIDA<sup>\*</sup>) showed normal hepatocyte function and normal emptying of the gallbladder.

Current therapy: the patient received 1 WBHT treatment, T rect.max. 41.9°C; plateau 2 hours at 41.8°C, within a series of radiotherapy which was stopped after 6 x 1.5 Gy had been given, when serious toxicity became evident. INH was administered from 1 week before WBHT to avoid recurrence of tuberculosis.

Toxicity: following WBHT massive liver necrosis occurred, resulting in the death of the patient 5 days later. The autopsy showed an extensively damaged haemorrhagic and necrotic liver with some vital liver cells in the periphery of the lobes only.

Objective tumour response: The autopsy showed some vital tumour metastases in the lungs and in the liver, which showed no signs of necrosis.

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\* HIDA: diethyl-iminodiacetic acid labelled with <sup>99</sup>Technetium (Solco Basle Ltd) is administered intravenously. In normal subjects, maximum uptake within the hepatocytes takes place within 15 minutes and filling of the gall bladder can be visualized by scanning within 40 minutes following intravenous administration.

#### CASE 19

A 44-year-old male, with a 2-month-history of tumour in the retroperitoneal space.

Histopathology: leiomyosarcoma.

Previous therapy: a laparotomy was performed when ileus occurred. Because the tumour was judged inoperable during surgery, various anastomoses were constructed to maintain gastrointestinal function.

Pretreatment status: a large retroperitoneal tumour, dimensions (determined by computer tomography) 15x15x20 cm, infiltrating the pancreas and 1 kidney, and comprising necrotic areas.

Current therapy: the patient received 1 WBHT treatment, T rect.max. 41.9°C; plateau 2 hours at 41.6°C, within a series of radiotherapy, 10 x 2 Gy in 2 weeks.

Toxicity: no special problems.

Objective tumour response: CT scanning 1 month following WBHT showed some tumour regression and two months following WBHT the tumour could be surgically removed, including the spleen and parts of the pancreas, ileum and colon. Histologic examination of the surgical specimen showed vital tumour tissue with edema and haemorrhages. At one site a fistula had been formed from a intratumour cavity through the intestinal wall.

Palliation: the pain had disappeared immediately following WBHT.

The patient was free of disease for a period of 1 year, at which point local recurrence and liver metastasis became evident.

The patient died 14 months following WBHT due to tumour progression within the abdomen (local recurrence and liver metastasis).

#### CASE 20

A 56-year-old female, with a 2-month-history of malignant tumour of the sigmoid.

Histopathology: adenocarcinoma.

Previous therapy: at laparotomy the tumour was judged to be inoperable and an entero-enterostomy was constructed.

Pretreatment status: a large tumour involving the bladder wall and para-aortic lymph nodes. There was no evidence of distant metastasis. The patient suffered from frequently recurring cystitis.

Current therapy: the patient received 2 WBHT treatments with a time interval of 7 weeks, each within a series of radiotherapy, 15 x 2.3 and 15 x 2 Gy re-

spectively. 5 FU was administered daily on the first 4 days of each radiotherapy series. Following the combined treatment series 5 FU injections were given once weekly.

WBHT 1: T rect.max. 41.7°C; plateau 2 hours at 41.7°C;

WBHT 2: T rect.max. 41.8°C; plateau 2 hours at 41.8°C.

Toxicity: following both WBHT treatments the patient incurred multiple second-degree burns of the extremities and the back.

Objective tumour response: CT scanning 2 months following WBHT showed "no change". The tumour was progressive 7 months following WBHT.

Palliation: none.

The patient died 10 months following WBHT due to local tumour progression.

#### CASE 21

A 51-year-old male with a 6-week-history of pleural tumour.

Histopathology: fibrous mesothelioma.

Previous therapy: none.

Pretreatment status: a lobulated pleural tumour which compressed the bronchial tree. The patient suffered severe pain in the thoracic wall. There was no evidence of distant metastasis.

Current therapy: the patient received 1 WBHT treatment, T rect.max. 42.0°C; plateau 2 hours at 41.8°C, within a series of radiotherapy 12 x 2 Gy in 3 weeks.

Toxicity: 2 days following WBHT the patient developed hemiparesis. CT scanning of the brain demonstrated that there were multiple brain metastases surrounded by a oedematous zone.

Objective tumour response: the tumour continued to progress.

Palliation: the pain disappeared immediately following WBHT.

The patient died 1 month later. Autopsy showed that there were extensive tumour masses in the pleural as well as in the abdominal cavity. The tumour showed aggressive infiltration, which is not common with this type of tumour.

#### CASE 22

A 57-year-old male, 9 years under treatment for a rectum tumour which had locally recurred.

Histopathology: poorly differentiated adenocarcinoma.

Previous therapy: surgery of the primary tumour with construction of a pre-

ternatural anus, followed 6 years later by excision of recurrent tumour. Radiotherapy combined with 5 FU for the area of recurrence. Chemotherapy (combination of 5 FU, oncovin and CCNU) and radiotherapy for various metastases.

Pretreatment status: large local recurrence within the pelvis, which was the cause of considerable pain and restricted mobility, and lung metastases.

Current therapy: the patient received 1 WBHT treatment, T rect.max. 41.8°C; plateau 2 hours at 41.8°C, within a series of radiotherapy: 10 x 1.5 Gy on the pelvic tumour; 5 x 2 and 4 x 2.5 Gy on the lung metastases.

Toxicity: no specific problems.

Objective tumour response: the pelvic tumour and the lung metastases showed "no change" for 5 and 6 months respectively.

Palliation: the pain largely disappeared; a palliative effect which lasted for 4 months.

The patient died 7 months following WBHT due to tumour progression.

#### CASE 23

A 38-year-old male presented with a tumour initiating from the paravertebral muscle. He had been suffering pain for 2 years, the existence of a tumour was known for 3 months.

Histopathology: leiomyosarcoma.

Previous therapy: irradiical surgery.

Pretreatment status: a large tumour of the dorsal abdominal wall, which caused much pain. There was no evidence for distant metastasis.

Current therapy: the patient received 2 WBHT treatments with a time interval of 2 weeks, within a series of radiotherapy 30 x 2 Gy.

WBHT 1: T rect.max. 41.9°C; plateau 2 hours at 41.8°C;

WBHT 2: T rect.max. 41.8°C; plateau 2 hours at 41.8°C.

Toxicity: no specific problems.

Objective tumour response: the tumour showed some regression, recorded as "no change", lasting 9 months.

Palliation: the pain disappeared completely following the first WBHT treatment a palliative effect which lasted 7 months. The paresis of one leg was transiently aggravated following WBHT.

Lung metastasis was discovered 10 months following WBHT and the patient died 23 months after the first WBHT.

#### CASE 24

A 56-year-old male with a gastric tumour, which was judged inoperable at laparotomy.

Histopathology: moderately differentiated adenocarcinoma.

Previous therapy: none.

Pretreatment status: a large tumour, infiltrating pancreas and colon. There was no evidence of distant metastasis.

Current therapy: the patient received 1 WBHT treatment, T rect.max. 42.0°C; plateau 2 hours at 41.8°C, within a series of radiotherapy, 10 x 2 Gy.

Toxicity: no specific problems.

Objective tumour response: the WBHT was followed by surgery 6 weeks later, during which the tumour could be completely excised including part of the pancreas; tumour infiltration of the colon was not detectable anymore.

The tumour recurred 2 years after surgery within the scar of the abdominal wall.

Palliation: the previously moderate pain became less severe following WBHT. The patient died 44 months following WBHT due to local tumour progression.

#### CASE 25

A 65-year-old female with a 20-month-history of kidney tumour.

Histopathology: adenocarcinoma.

Previous therapy: irradical surgery of the primary tumour, followed by radiotherapy.

Pretreatment status: multiple lung metastasis.

Current therapy: the patient received 2 WBHT treatments with a time interval of 3 weeks, within a series of radiotherapy 8 x 2.5 Gy on the mediastinum and 10 x 1.5 Gy on the remaining parts of the lungs.

WBHT 1: T rect.max. 41.9°C; plateau 2 hours at 41.8°C;

WBHT 2: T rect.max. 41.9°C; plateau 2 hours at 41.8°C.

Toxicity: following the first WBHT the patient developed herpes simplex of the lip, extending through the nose to one eye. The second WBHT was delayed 1 week until this infection had healed. Following the second hyperthermia, the puncture site in the femoral vein continued coozing for 10 hours. It was found that thrombopenia had developed (lowest count  $30 \cdot 10^9/L$ ), together with a decrease in fibrinogen serum level (lowest level 2.6 g/L), and an increased Prothrombin Time (21 seconds; standard 13 seconds). FDP remained below 10 mg/L. This combination of findings made the diagnosis disseminated intravascular coagulation

(DIC) probable. (Kobayashi et al. 1983). Following transfusion of thrombocytes coagulation parameters rapidly recovered and the puncture site stopped bleeding.

Objective tumour response: there was less than partial regression of the metastatic nodules. This "no change" lasted for 3½ months at which point the patient developed carcinomatous pleuritis.

Palliation: not applicable.

The patient died 5 months following WBHT due to progression of carcinomatous pleuritis.

#### CASE 26

A 51-year-old female with a 7-month-history of tumour of the kidney, which had metastasized to the lungs.

Histopathology: adenocarcinoma.

Previous therapy: radical surgery of the primary tumour, radiotherapy of various metastases (excepting lung metastasis), hormonal therapy (niagestin and prednison).

Pretreatment status: multiple lung metastases.

Current therapy: the patient received 1 WBHT treatment, T rect.max. 42.1°C; plateau 2 hours at 41.9°C, within a series of radiotherapy, 10 x 1.5 Gy.

Toxicity: 10 minutes before the end of the plateau phase, the ECG started showing periods of asystole. After interruption of WBHT and start of cooling, the ECG rapidly returned to normal. After WBHT, spontaneous ventilation was inadequate and artificial ventilation was necessary for a period of 36 hours.

Objective tumour response: the lung metastases showed "no change" for 2 months.

Palliation: not applicable.

The patient died 10 weeks following WBHT due to progression of lung metastasis.

#### CASE 27

A 69-year-old male with a 1-year-history of tumour initiating from the pleura.

Histopathology: malignant mesothelioma.

Previous therapy: palliative draining of pleural effusion.

Pretreatment status: a large tumour extending over the entire pleural cavity and in the thoracic wall, which caused much pain. The lung function was



reasonable.

Current therapy: the patient received 1 WBHT treatment, T rect.max. 42.1°C; plateau 2 hours at 41.9°C, combined with only 1 of the 12 planned 2 Gy fractions of radiotherapy.

Toxicity: from a few hours following WBHT, the patient developed an adult respiratory distress syndrome, with fatal outcome 1 week after WBHT.

Objective tumour response: post mortem investigation showed multiple distant metastases with central necrosis. The primary tumour had infiltrated the pericard and also showed necrotic areas.

Palliation: the patient reported that the pain in the thoracic wall had completely disappeared following WBHT.

#### Summary of the patient series

The first impression of this patient material is that WBHT appears worthwhile especially when combined with radiotherapy and that in patients who suffer pain of a tumour in a previously irradiated area. Following WBHT alone or in combination with chemotherapy, no impressive results were observed. Most patients had tolerated the WBHT treatment with minor problems only, but a few patients had to deal with severe toxicity. Two patients even died as a result of the treatment, which made us decide to discontinue this clinical study.

In this series of 27 patients it is curious to note that in the earlier patients the toxicity was relatively mild and seemed avoidable with growing experience and the therapeutic results were promising, while in the second half the major toxicities occurred and the number of objective responses decreased. It was not possible to demonstrate a conclusive explanation for this chronological worsening of results.

In the following chapter, the results will be presented and discussed in detail.



# RESULTS

## Chapter VI

### 1) Efficiency of heating technique

Efficiency of heating techniques can be measured by the following parameters:

- the heating rate, which has to be as high as possible in order to reduce treatment time and to minimize the induction of thermotolerance;
- the heat dose, which has to be high enough to achieve a therapeutic effect, but should not exceed the body's tolerance;
- the temperature distribution, which has to be as homogeneous as possible in order to achieve an optimal dose at each tumour localization.

Three separate heating methods that have been explored can be distinguished in this series, i.e.:

- 1) warm air (60-65°C) only;
- 2) warm air combined with water-impermeable plastic foil covering the skin;
- 3) warm air combined with plastic foil and warm water mattress (44-46°C).

These techniques yield relevant differences with regard to the time required to increase the temperature and to the homogeneity of temperature distri-

bution.

### Heating rate

For the evaluation of heating rate, the time required to increase the rectal temperature from 38 to 41°C (in °C/hour) was chosen as the most representative for temperature increase. This was done because the temperature at which heating was started varied from 35.9 to 38.9°C. The lowest starting temperature was recorded at the first treatment of patient no. 2, where no measures had been taken to prevent cooling. The highest starting temperature was observed in patient 9-1, where the time between induction of anaesthesia, isolation with plastic foil, administration of warmed inhalation gases and infusion fluids and the "start" of heating by closing the cabin, was much longer than usual due to technical problems. The temperature of 41°C was chosen as upper limit for this evaluation of heating rate, because over this temperature measures were taken to decrease energy input to the patient in order to avoid overshoot of temperature. The relevant parameters for heating rate are listed in Table VI-1. Unfortunately, the temperature data of 3 treatments were lost and therefore lack in the evaluation. Patient no. 1, in whom WBHT was combined with additional local hyperthermia is also excluded from this analysis. The temperature at which heating was started was significantly higher in the patients treated with method 3. In fact, heating was already under way before the hood of the cabin was closed, i.e. during the period that all monitoring lines were placed. This was by energy input from the water mattress to the skin of the back and by isolation of the body with an aluminium blanket. There were no significant differences between the three groups of patients with regard to body weight or body surface area, so that differences in heating rates indeed can be judged as real differences.

The heating rate was found to vary from 1.64 to 1.89 °C/hour with method 1, from 1.38 to 2.65 °C/hour with method 2 and from 2.00 to 3.60 °C/hour with method 3. (See table VI-I). The mean heating rate for method 1 is not significantly lower than that for method 2. Using method 3, the heating rate was found to become significantly higher, reaching a mean value of 2.69 °C/hour. As the heating rate can be expected to depend on body weight as well as on body surface area, the degree of association between these factors was investigated by calculating the correlation coefficients, for methods 2 and 3 (with method 1, the number of data pairs was only 4). These correlation coefficients are listed in table VI-2.

In the group of patients treated with method 2 (n = 9), negative correlations

Table VI-1 PARAMETERS RELEVANT TO HEATING RATE ACHIEVED BY THE VARIOUS TECHNIQUES USED

	Technique 1 <sup>*1</sup>			Technique 2 <sup>*1</sup>			Technique 3 <sup>*1</sup>		
	mean	s.d.	n <sup>*2</sup>	mean	s.d.	n <sup>*2</sup>	mean	s.d.	n <sup>*2</sup>
temperature at start heating (°C)	36.6	0.5	4	36.9	0.5	9 <sup>*3</sup>	37.4	0.5	25
body weight (kg)	65.5	7.7	4	67.2	7.3	12	64.7	11.1	26
body area (m <sup>2</sup> )	1.77	0.22	4	1.77	0.14	12	1.77	0.16	26
heating rate (°C/min; 38 → 41°C)	1.78	0.10	4	1.97	0.49	9	2.69	0.45	24
time to reach 41.5°C from start heating (min)	203	29	4	171	26	9	116	23	24
number of patients	3			5			18		

\*1 technique 1: warm air only; technique 2: warm air and plastic foil; technique 3: warm air, plastic foil and warm water mattress.

\*2 n: the number of data available.

\*3 1 treatment with starting temperature of 38.9°C excluded.

Table VI-2 ASSOCIATION BETWEEN HEATING RATE AND PATIENT PARAMETERS

correlation investigated	technique 2 (n=9)		technique 3 (n=24)	
	r	2p	r	2p
HR vs BW	-0.763	<0.05	-0.154	>0.1
HR vs BSA	-0.672	<0.05	-0.069	>0.1
HR vs BW/BSA	-0.642	<0.1	-0.206	>0.1

HR = heating rate ( $^{\circ}\text{C}/\text{hour}$ ); BW = body weight (kg); BSA = body surface area ( $\text{m}^2$ ); BS/BSA = ratio of body weight and body surface area ( $\text{kg}/\text{m}^2$ ); r = correlation coefficient.

( $r = -0.642$  to  $-0.763$ ) were found between heating rate and body weight, body surface area and the ratio between body weight and body surface area, respectively. These correlation coefficients were statistically significant for the association between heating rate and body weight, and heating rate with body surface area, respectively. In the larger group however, treated with method 3 ( $n = 24$ ), these relations were, surprisingly, less clear; correlation coefficients varied from  $-0.069$  to  $-0.206$ . This last, largest, value was found for the relation between heating rate and the ratio of the two patient parameters, but this was not statistically significant.

These insignificant relations between heating rate and patient parameters could also be demonstrated by the values for heating rate of individual patients, which showed ranges as large as  $2.25 - 3.27^{\circ}\text{C}/\text{hour}$  for two successive treatments in one patient (case no 20, first and second treatment). The overall time required to reach  $41.5^{\circ}\text{C}$  from the start of heating was found to show even more variation. The mean overall time in patients heated by method 1 (mean starting temperature  $36.6^{\circ}\text{C}$ ) was 203 minutes, 32 minutes more than with method 2 (mean starting temperature  $36.9^{\circ}\text{C}$ ) and even almost 90 minutes more than with method 3 (mean starting temperature  $37.4^{\circ}\text{C}$ ).

#### Heat dose

The heat dose achieved, expressed as mean rectal temperature during plateau phase, had a mean value of 2 hours at  $41.8^{\circ}\text{C}$  for 40 of 45 treatments. The

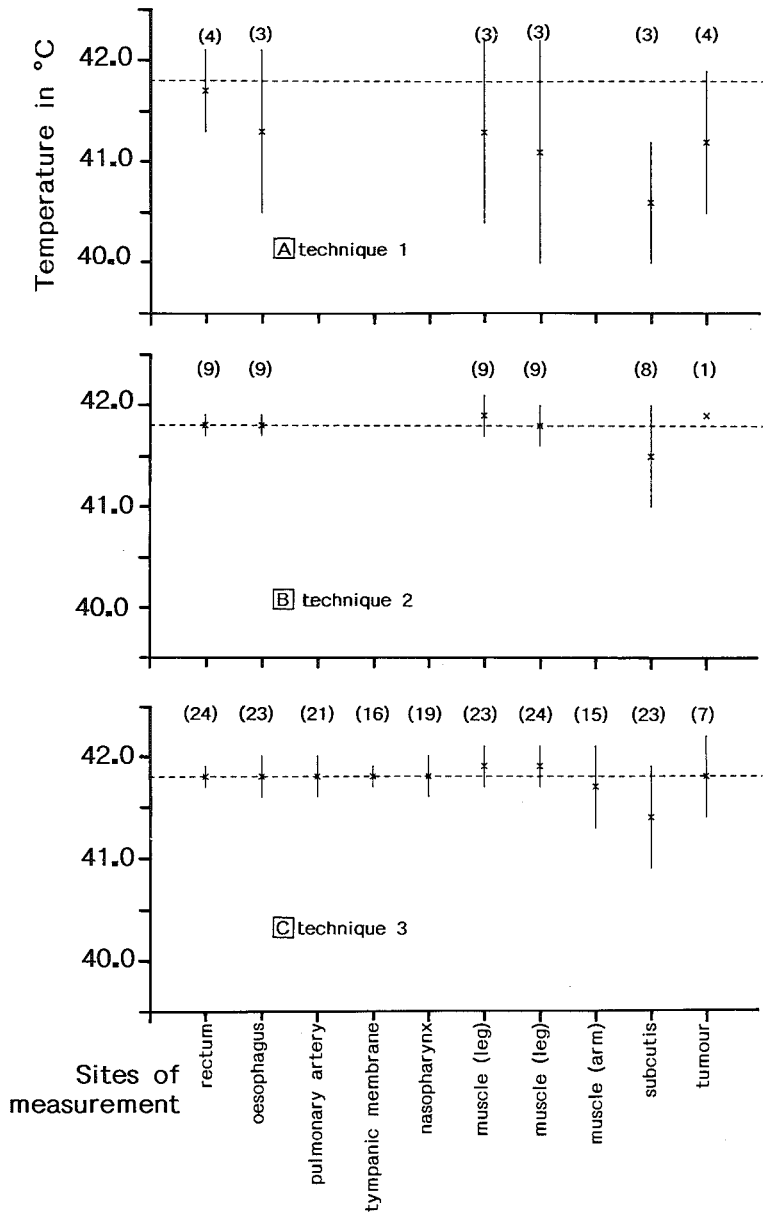


Fig. VI - I TEMPERATURE DISTRIBUTION DURING PLATEAU PHASE

Temperature distribution during the plateau phase of WBHT achieved with the various techniques used. Technique 1: warmed air only; technique 2: warm air and plastic foil; technique 3: warm air, plastic foil and warm water mattress. The figure shows the means and s.d.'s, the number of treatments are given in brackets.

Temperature in °C

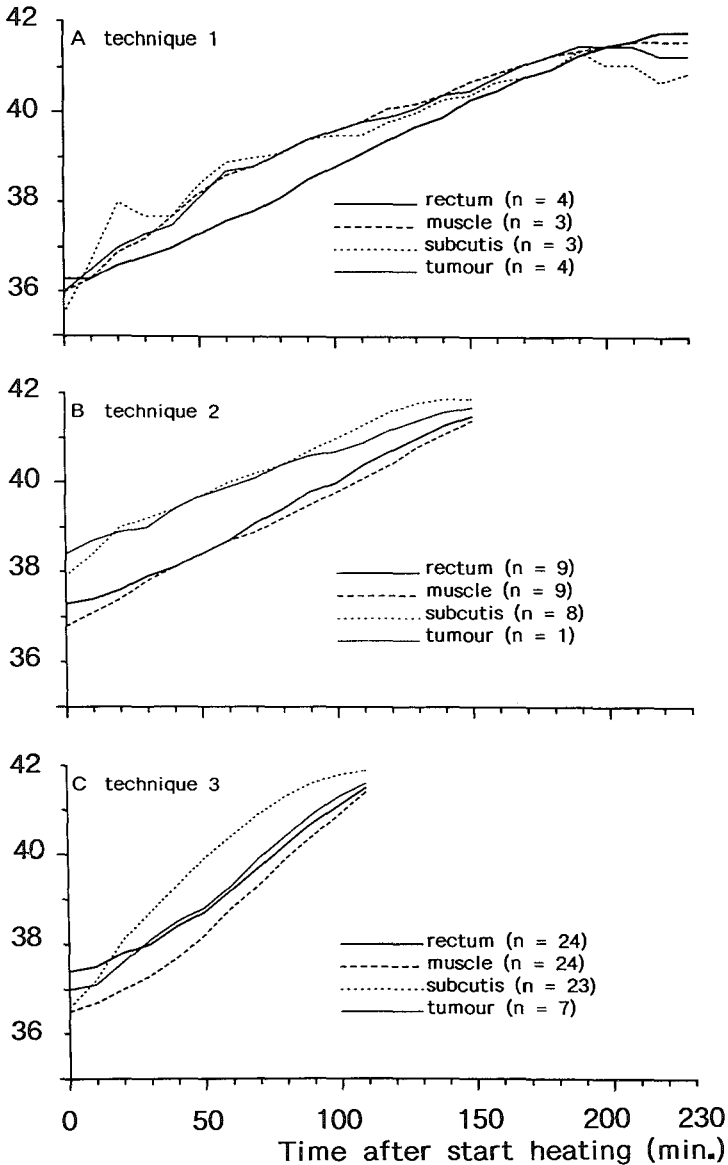


Fig. VI - 2 TEMPERATURE DISTRIBUTION DURING THE HEATING PHASE

Temperature distribution during the heating phase of WBHT achieved with the various techniques used (1: warm air only; 2: warm air and plastic foil; 3: warm air, plastic foil and warm water mattress). The figure shows the mean courses of temperature, with the number of treatments in parenthesis.



range in mean rectal temperature during plateau phase was found to be small, 41.7-42.1°C, resulting in a standard deviation of only 0.09°C.

During 5 treatments the heat dose administered was purposely differently. Patients nos 1 and 19 received lower heat doses. Patient no. 1 was given three treatments of 140 minutes at 40.1°C, 150 minutes at 41.2°C and 210 minutes at 41.4°C, respectively. This was done as a way of precaution. Patient no 19 received one treatment of 2 hours at 41.6°C as we feared a toxic overload should his massive tumour which showed ill-perfused areas as judged by CT-scanning, suddenly might become necrotic.

Patient no.16 received a third treatment of 3 hours at 41.8°C. The experience regarding toxicity obtained in previous patients and in this particular patient during the first and second treatment made us venture upon giving her a third WBHT treatment with prolonged treatment time. The short heating time achieved with method 3, made that this prolonged treatment could be performed within a normal working day. This last condition was important with regard to the post-WBHT care for the patient which had to be provided by the intensive care unit and the laboratory staff.

#### Temperature distribution

The temperature distribution during plateau phase maintained by the various techniques is shown in figure VI-1 (A, B and C). Using warm air only the variation between temperatures at the various measuring sites is very large. The mean value for rectal temperature in this group is 41.7°C. The 0.3°C lower oesophageal temperature is probably due to improper placement (insufficiently deep) of the probe in the oesophagus in 3 of the 4 treatments. At insufficient depth in the oesophagus, the temperature is influenced by the temperature of respiration gases which were not warmed in these patients.

The intramuscular and subcutaneous temperatures during plateau phase were 0.4 to 1.1°C lower than rectal temperature. The situation was reversed during the heating phase in this group: muscle, subcutaneous and tumour temperature were found to be mean 0.5°C higher during heating than the rectal temperature (figure VI-2A).

The sharp decrease in heating rate of the subcutaneous tissue after 20 minutes heating shown in this figure may be caused by the increase in blood flow through the skin. Figure VI-1B shows that temperature distribution is much more homogeneous when plastic foil is used. The maximum temperature difference is that between rectum and subcutaneous tissue, being 0.3°C. The same is demonstrated in figure VI-1C for method 3.

With methods 2 and 3, during the heating phase the intramuscular temperature was found to be somewhat lower than the rectal temperature; whereas the subcutaneous temperature was, again, higher.

The temperatures measured in the tumour depend on the tumour localization; the temperatures of superficial tumours reflect subcutaneous temperature, whereas tumours seated deeper than 1 cm below the skin surface reflect rectal temperatures, also during the heating phase.

Liver temperature could be measured in one patient (no. 27). This was performed with a custom-made small thermocouple probe built into the tip of the hepatic vein catheter by the physicist of our department (Ing. G.C. van Rhoon). Unfortunately this probe broke 55 minutes after the start of plateau phase, when the catheter was manipulated to regain the possibility of draining blood from the hepatic vein. The liver temperature measurements therefore were limited to the first 155 minutes of the WBHT treatment. The temperatures recorded from the oesophagus, the rectum and the liver respectively are presented in figure VI-3. At the start of heating, no difference between rectal, liver and oesophageal temperature, respectively, was found (the 0.1°C higher

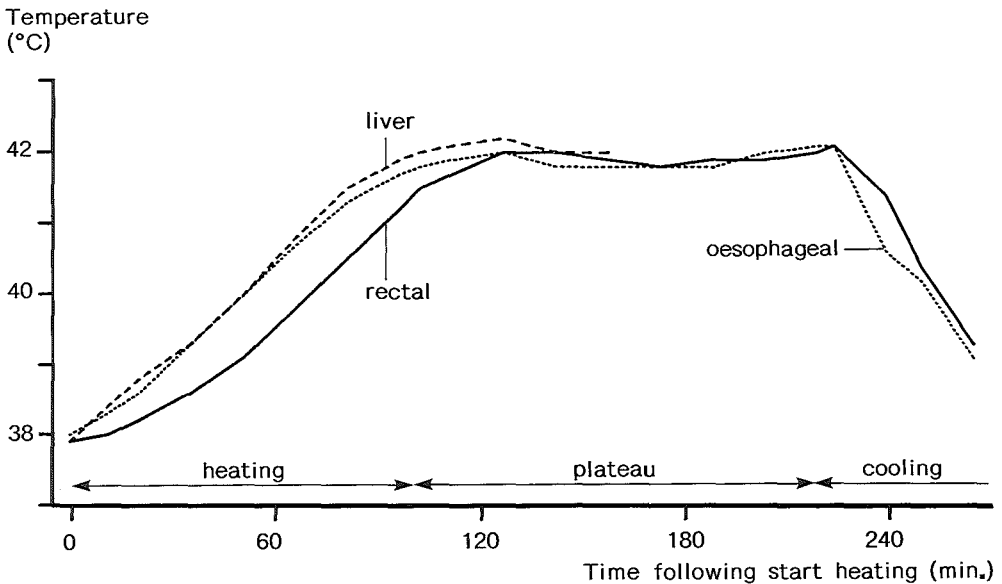


Fig. VI - 3 COURSE OF LIVER TEMPERATURE DURING WBHT

Course of liver -, rectal - and oesophageal temperature during WBHT in patient no. 27.

temperature in the oesophagus is within the accuracy range of the probes). During the heating phase, a difference between liver and rectal temperature was observed which increased with increasing heating time up to a maximum value of  $1.0^{\circ}\text{C}$  at 80 minutes from the start of heating. During the heating phase, the liver temperature was on the average  $0.66^{\circ}\text{C}$  higher than the rectal temperature. This difference was found to decrease again after the lowering of energy input. From the start of plateau phase the difference between liver and rectal temperature decreased further to become zero at 40 minutes after the start of plateau phase.

The oesophageal temperature was observed to be close to liver temperature during the heating phase (maximum difference  $0.2^{\circ}\text{C}$ , mean difference  $0.09^{\circ}\text{C}$ ), but became consistently  $0.2^{\circ}\text{C}$  lower than the liver temperature, from the time that the energy input was decreased till the end of hepatic vein temperature measurement. Figure VI-3 also shows the rectal temperature lagging behind the oesophageal temperature during the heating phase, which was the course observed usually. The maximum difference between rectal and oesophageal temperature was  $0.9^{\circ}\text{C}$ , between 60 and 75 minutes from the start of heating. This difference had become zero again at 25 minutes after the start of the plateau phase.

Additional local heating by means of 433 MHz microwaves indeed resulted in higher tumour temperatures, as was demonstrated in patient no. 1. The mean tumour temperatures achieved were  $1.0 - 1.7^{\circ}\text{C}$  higher than the mean rectal temperature during the plateau phase (see table VI-3). Figure VI-4 gives an example of the additional local tumour heating and the temperatures achieved during the second treatment of patient no. 1. This combination of WBHT and local hyperthermia could be performed without complications during the first and second treatment of patient no. 1. During the third treatment however, suddenly a sharp increase in tumour surface temperature, as measured by LOOF, was observed. This happened following a period of uneventful treatment. Up to 381 minutes of treatment, being 160 minutes at plateau the tumour temperature had not exceeded  $43.4^{\circ}\text{C}$ . The following 14 minutes, tumour temperatures increased up to  $45.0^{\circ}\text{C}$ , and then in the next one minute, the LOOF reading suddenly increased to values above its calibration range. The corresponding temperature was estimated to be about  $55^{\circ}\text{C}$ . The treatment was stopped and the patient later developed a severe third degree burn of 10 cm diameter. This lesion included necrosis of an area of rib cartilage.

The cause of the sudden high temperature increase may have been a standing wave, while the increased temperature in turn may have caused a secondary

Table VI-3 TEMPERATURES ACHIEVED WITH LOCAL HT IN ADDITION TO WBHT

	Rectal temperature ( $^{\circ}\text{C}$ )		Tumour temperatures	
	mean <sup>*1</sup>	maximum	mean <sup>*1*2</sup> (range)	maximum <sup>*2</sup> (range)
1 <sup>st</sup> treatment	40.1	40.4	41.6 (41.4-41.8)	42.8 (42.3-43.3)
2 <sup>nd</sup> treatment	41.2	41.4	42.9 (42.5-43.5)	45.7 (44.1-46.7)
3 <sup>rd</sup> treatment	41.4	41.6	42.4 (42.2-42.5)	46.6 (43.4- >55)

\*1 mean temperature over the "plateau phase"

\*2 mean value for 2,3 and 4 tumour temperatures measured during the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> treatment respectively.

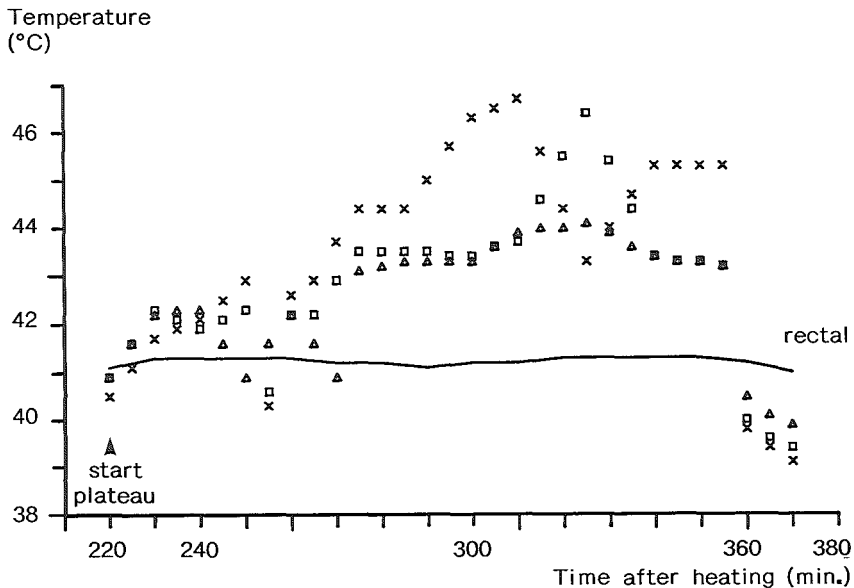


Fig. VI - 4 TEMPERATURE DISTRIBUTION DURING ADDITIONAL LOCAL HEATING

Rectal temperature and tumour temperatures ( $\square$  and  $\Delta$  : tumour center;  $\times$  : tumour periphery) during plateau phase during the second WBHT treatment in patient no. 1.

stoppage of the local circulation. Obviously, tumour temperature control had failed.

### Summary

Combining the original heating system of the cabin, e.g. warm air, with covering of the skin by plastic foil and extra energy input via the skin of the back yields a gain of about 1½ hour in achieving the set point temperature.

The use of plastic foil over the entire body area was found to result in a more homogeneous temperature distribution through the whole body, which is important during treatment of patients with metastasized tumours.

### Physiology

#### Tumour pH

Intratumoural pH was determined in 4 patients during 7 WEHT treatments.

In case 9, one electrode was placed into the pelvic metastasis of a mammary carcinoma ulcerating through the vaginal wall. In case 10 (locally recurrent colon adeno carcinoma), 2, 1 and 2 electrodes were placed during the 1st, 2nd and 3rd WEHT session respectively, in the tumour ulcerating through the abdominal wall. In case 13 (adenocystic carcinoma), 1 electrode was introduced through the intact mucosa in the tumour protruding in the oral cavity. In case 15 (locally recurrent squamous cell carcinoma of the uterine cervix), measurements were done during both WEHT sessions within the tumour infiltrating subcutaneously in the abdominal wall. The results of these pH determinations during plateau and cooling phase are given in figure VI-5. No significant changes in tumour pH values were observed during the plateau phase of the WEHT treatment. As mentioned before (chapter V), the values obtained during the heating phase were considered unreliable.

In patient 10, the tumour pH measured during the second WEHT treatment is considerably higher than its value during the first and third treatment, respectively. In patient 15, the mean of 2 measured tumour pH values was somewhat higher during the second treatment than during the first treatment.

Eleven subcutaneous pH measurements were performed, in patients no. 9 (1 measurement), 15 (1 measurement during the second treatment), 16 (2 measurements during the first and third treatment, respectively), 17 (1 measurement), 18 (2 measurements) and 19 (2 measurements). The pH of arterial blood samples was determined regularly as described in chapter V. A comparison of tumour pH, subcutaneous pH and arterial pH for each patient treatment is given

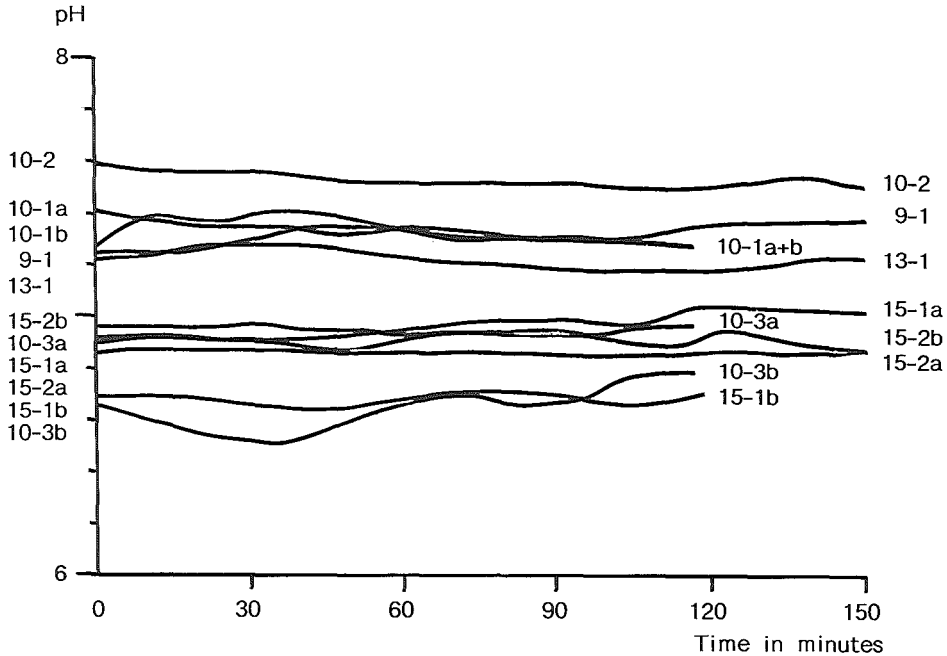


Fig. VI - 5 COURSE OF TUMOUR pH DURING WBHT

Course of tumour pH in 4 patients during 7 WBHT treatments. Time = 0: start plateau phase; time = 120: start cooling. Patient number and treatment number is indicated with the curves.

in table VI-4. Subcutaneous pH was measured simultaneously with tumour pH during the WBHT treatments in patients no. 9 and no. 15 (second treatment), and was higher than tumour pH in both cases (mean difference 0.31). Subcutaneous pH (either the mean of 2 determinations or 1 determination during one treatment, respectively) was also higher than arterial pH (at start plateau) in all of the paired measurements, the mean difference was found to be 0.21. This difference was found to be significant (paired T-test,  $2p < 0.001$ ). Subcutaneous pH was observed to decrease during the plateau phase in 9 of 11 determinations. The difference between subcutaneous pH at the start and the end of the plateau phase respectively was found to be 0.08 and was statistically significant ( $2p < 0.025$ ). The difference between arterial pH and tumour pH was also significant (paired T-test,  $2p < 0.001$ ). No changes in arterial pH were observed during the plateau phase. A comparison of the mean pH values measured at start and end of plateau phase in tumour, subcutis and arterial blood, respectively, is given in figure VI-6.

Table VI-4 COMPARISON OF TUMOUR, SUBCUTANEOUS AND ARTERIAL PH DURING WBHT

Patient No. treatment no.	Histology	tumour pH		subcutis pH		arterial pH	
		Start plateau	Start cooling	Start plateau	Start cooling	Start plateau	Start cooling
9-1	breast adenoca	7.25	7.36	7.44	7.47	7.26	7.35
10-1	colon adenoca	7.41; 7.27	7.28; 7.28			7.28	7.28
-2*(1)		7.59	7.51			7.38	7.41
-3*(2)		6.92; 6.66	6.97; 6.79			7.33	7.32
13-1	pharyngeal adenocystous ca	7.22	7.23			7.53	7.49
15-1	cervical squamous cell ca	6.90; 6.69	7.04; 6.71			7.37	7.29
-2*(3)		6.86; 6.96	6.86; 6.94	7.49	7.39	7.34	7.32
16-1	colon adeno			7.43; 7.76	7.38; 7.55	7.41	7.43
-3*(4)				7.50; 7.84	7.43; 7.75		7.36
17-1	lung adenoca			7.47	7.40	7.32	7.31
18-1	adenocystous ca			7.97; 7.45	7.76; 7.31	7.50	7.45
19-1	leiomyosarcoma			7.74; 7.50	7.67; 7.54	7.54	7.53
	mean	7.066	7.088	7.599	7.514	7.387	7.378
	S.E.M.	0.091	0.078	0.047	0.045	0.029	0.024

There is no significant difference in pH values at start plateau and at start cooling for tumour and arterial blood; a paired T-test gave 2p values of 0.41 for the tumour pH and 0.84 for the arterial pH. The difference between tumour and arterial pH is significant (2p = 0.0001). The subcutaneously measured pH decreases significantly during plateau phase (2p < 0.025). Subcutaneous pH is higher than arterial pH (2p < 0.001).

\*time interval from previous WBHT (1) 2 weeks (2) 3 months (3) 1 week (4) 4 weeks.

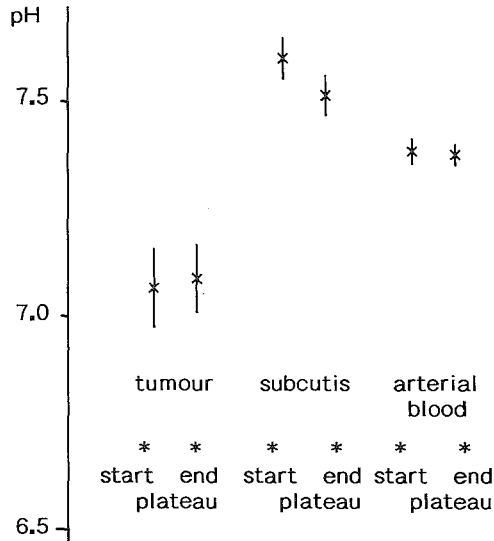


Fig. VI - 6 pH CHANGES DURING PLATEAU PHASE OF WBHT

Changes in tumour, subcutis and arterial blood pH during the plateau phase of WBHT. In this figure the means and SEM's are given. For details, see table VI-3.

#### Cardiovascular changes during WBHT-treatment

Changes in cardiovascular functions have been reported extensively elsewhere (Faithfull 1983, Faithfull et al. 1984). Changes observed in some of the parameters can be summarized as follows:

(1) the pulse rate increased from a mean of 63 beats/min before induction of anaesthesia to a maximum of 146 at the end of the plateau phase; (2) the mean systemic arterial pressure decreased from a mean of 88 mmHg to a mean lowest value of 61 mmHg after 15 minutes of cooling. Most patients were relatively hypotensive during cooling and for a few hours following WBHT; (3) the cardiac output increased from a mean of 5.75 L/min at the start of heating to a mean of 12.67 L/min during the plateau phase; (4) the arterial pH during the plateau phase ranged from 7.24 to 7.53, with a mean value of 7.39.

The large increases in cardiac output and heart rate were accompanied by large decreases in peripheral resistance in both the systemic and pulmonary vascular beds. The pulmonary arterial pressure rose whereas that in the systemic circulation fell. This caused right ventricular work to increase proportionally more than left ventricular work.



## Response

### Objective tumour response

#### a) Following WBHT alone (Table VI-5)

Following WBHT alone, none of the patients (cases 1,2,3,4,9 and 12) showed an objective tumour response, although some regression was observed in a few patients.

During the first WBHT session in case 2, a change in the formerly red colour of the midsternal cutaneous nodule to blue was observed, probably due to stasis in blood vessels. This nodule showed an immediate regression of 56%, but three weeks later regrowth at the margins of the tumour was observed.

In case 3, 20% regression in the size of cutaneous metastatic nodules was observed, but progression occurred also after 3 weeks.

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Table VI-5 RESULTS FOLLOWING WBHT ALONE

<u>tumour</u>	<u>case</u>	<u>result</u>
breast ca	1	no effect
	2	"no change" 3 weeks (56% regression)
	9	no effect
malignant melanoma	3	"no change" 3 weeks (20% regression)
	4	"no change" 3(+) months
osteosarcoma	12	"no change" 6 weeks

---

#### b) Following WBHT and chemotherapy (Table VI-6)

Two patients with breast adenocarcinoma (cases 1 and 2) were treated in combination with melphalan. In both patients "no change" was observed lasting for 3 months and 2 months, respectively.

Two patients with colon adenocarcinoma (cases 10 and 16) and one patient with bronchial adenocarcinoma (case 17) were treated in combination with 5 FU. Only in patient no 16 a "partial response" was observed which lasted, during continuous administration of 5 FU once weekly, for two months. In cases 10 and 17 "no change" was observed for 6 months and 1 month, respectively.

Table VI-6 RESULTS FOLLOWING WEHT AND CHEMOTHERAPY

	<u>case</u>	<u>tumour</u>	<u>result</u>
melphalan:			
	1	breast ca	"no change" duration 3 months
	2	" "	"no change" duration 2 months
-----			
5 FU:			
	10	colon ca	"no change" duration 6 months
	16	" "	"partial response" duration 2 months
	17	bronchial adenoca	"no change" duration 1 month

c) Following WEHT and radiotherapy

Tumour response following WEHT combined with radiotherapy was evaluable in 17 of 22 patients. An overview of the results is given in table VI-7. Tumour response was found not evaluable in cases no 9, 18, 19, 24 and 27.

Patient no 9 died 3 weeks after WEHT treatment. At post mortem examination it was found that the previously large tumour in the pelvis had regressed completely and was macroscopically undetectable.

Patients no 18 and 27 died 5 and 7 days, respectively, following WEHT as a result of the treatment. Post mortem examination showed in patient no 18 no signs of tumour necrosis, whereas in patient 27 central necrosis was found within the (many) distant metastases.

Patients no 19 and 24 were both considered inoperable before treatment with WEHT and radiotherapy, 10 x 2 Gy. Two months and 6 weeks after WEHT, respectively, in both patients the tumour could be surgically removed.

Of the 17 evaluable patients, 8 had received WEHT in combination with a low dose of radiotherapy (15-24 Gy). In 4 of these patients, the total radiotherapy dose given had to be low because of previous irradiation (cases 8, 10, 15 and 22). In the other half of this group, the radiotherapy was given to one or both lungs and the dose was therefore limited to maximum 24 Gy. In this low radiotherapy dose group, the results found were: 1/8 "CR" (mesothelioma); 2/8 "PR" (previously irradiated rectum and colon

Table VI-7 RESULTS FOLLOWING WBHT AND RADIOTHERAPY

Tumour	case	radiotherapy total dose (fraction size)(Gy)	result
malignant melanoma	4	30 (5)	NC 2 months
lung adenoca	5	49 (2)	CR 10(+) "
	6	50 (2.5)	CR 11(+) "
lung squamous cell ca	7	46 (2)	PR 12 "
uterine cervix squamous cell ca	15	20 (2)	NC 2 "
mesothelioma	11	19.5 (1.5)	CR 21 "
	21	24 (2)	progression
	27	2 (2)	not evaluable
adenocystous carcinoma	13	55-65 (2.5)	CR 72(+)months
	18	9 (1.5)	not evaluable
osteosarcoma	12	67 (2/1.5)	NC 1 month
fibrosarcoma	14	60 (2)	PR 3 months
leiomyosarcoma	19	20 (2)	not evaluable(inop→op*)
	23	60 (2)	NC 9 months
breast adenoca	9	18 (2)	not evaluable (complete regression)
kidney adenoca	25	15-20 (1.5-2.5)	NC 4 months
	26	15 (1.5)	NC 2 "
gastric adenoca	24	20 (2)	not evaluable (inop→op*)
rectal adenoca	8	20 (2)	PR 1 month
	22	15-20 (1.5-2.5)	NC 5/6 months
colon adenoca	10	19.5 (1.5)	PR 3 "
	20	64.5 (2.3/2)	NC 7 "

\* (in)op : (in)operable

carcinoma), 4/8 "NC" (1 uterine cervix squamous cell carcinoma, 2 kidney adenocarcinoma and 1 rectum adenocarcinoma) and 1/8 progression (mesothelioma).

Nine patients were treated in combination with higher doses of radiotherapy (30-67 Gy). In this group the results were found to be as follows: 3/9 "CR" (2 lung adenocarcinoma, 1 adenocystous carcinoma); 2/9 "PR" (lung squamous cell carcinoma, fibrosarcoma) and 4/9 "NC" (malignant melanoma, osteosarcoma, colon adenocarcinoma, leiomyosarcoma). Some observations are noticeable in these patients:

- in case 5, complete regression was observed already after only 24 Gy + 3 WBHT sessions;
- in case 4, the previously irradiated group of lymph nodes showed "no change", whereas the previously non irradiated group of lymph nodes showed "partial response";
- in case 14, partial regression was observed after only 20 Gy in combination with 1 WBHT session. One month after completion of the radiotherapy series however, the tumour was observed to start regrowth from the margins of the radiotherapy field.

A summary of these results is given in Table VI-8.

---

Table VI-8 SUMMARY OF RESULTS FOLLOWING WBHT AND RADIOTHERAPY

<u>dose of X-rays</u>	<u>Progression</u>	<u>NC</u>	<u>PR</u>	<u>CR</u>
15 - 24 Gy	1/8	4/8	2/8	1/8
30 - 67 Gy		4/9	2/9	3/9
15 - 67 Gy	1/17	8/17	4/17	4/17

---

In 4 patients it was possible to make a comparison between radiotherapy only and radiotherapy combined with WBHT. The radiotherapy only was mostly given in an earlier stage of disease. These results are given in Table VI-9.

In all but one cases, the radiotherapy total dose given was considerably smaller when given in combination with WBHT than when given without WBHT,

Table VI-9 RADIOTHERAPY + WBHT IN COMPARISON WITH RADIOTHERAPY ALONE

RECTAL ADENOCARCINOMA

case 22	primary	69 Gy + 5 FU	PR 3 months
	local recurrence	15 Gy + WBHT	NC 5 months
	lung metastasis	30 Gy	4% regression (NC)
	lung metastasis	20 Gy + WBHT	14% regression (NC)
case 8	primary	60 Gy	NC 5 months
	local recurrence	20 Gy + WBHT	PR 6 weeks

-----  
COLON ADENOCARCINOMA

case 10	primary	52 Gy	PR 4 months
	local recurrence	19.5 Gy + WBHT	PR 3 months

-----  
LUNG ADENOCARCINOMA

case 5	lymph nodes	50 Gy	PR 6 months
	lymph nodes	46.5 Gy + WBHT	CR 10(+) months

whereas the effects on the tumour obtained are about equal. In case 5, where the tumours treated are well comparable (in both treatment regimens previously non irradiated supraclavicular lymph nodes were involved), the result of the combined treatment is clearly superior to the result of radiotherapy alone.

Palliative effect

In 16 patients, pain was an important symptom of their disease. The palliative effect following WBHT alone and following WBHT plus chemotherapy was evaluable in case 1. The palliative effect of WBHT plus radiotherapy and of WBHT plus chemotherapy was evaluable in case 10. The patients and the palliative effect of treatment are listed in table VI-10.

Severe or disabling pain was present in 12 patients. In 2 of these cases WBHT was given in combination with chemotherapy. The palliative effect in these two

cases was found to be none and minimal, respectively.

Ten of the cases with severe or disabling pain were treated in combination with radiotherapy. In 7 of these patients the observed pain relief was complete, for a duration ranging from 1 week to 3 months. It was remarkable that all these patients experienced the absence of pain immediately after recovery

Table VI-10 PALLIATION FOLLOWING WBHT

case no	WBHT combined with <sup>*1</sup>	severity <sup>*2</sup> of pain	palliative effect <sup>*3</sup> and duration	immediate following WBHT
1	-	<u>+</u>	-	
1	chemo	<u>+</u>	-	
2	-	<u>+</u>	+ 2 months	+
7	-	<u>+</u>	+++ 3 weeks	
8	RT	+++	+++ 3 weeks	+
9	RT	+++	+++ 3 weeks (+)	+
10	RT	+++	+++ 2 months	+
10	chemo	++	<u>+</u> 6 months	
14	RT	+++	+++ 3 months	+
15	RT	++	<u>+</u> 2 months	
16	chemo	++	-	
19	RT	++	+++ 2 months (surgery)	+
20	RT	+	-	
21	RT	++	+++ 1 month (+)	+
22	RT	+++	++ 4 months	
23	RT	++	++ 7 months	+
24	RT	+	+ 2 years	
27	RT	++	+++ 1 week (+)	+

<sup>\*1</sup> RT: radiotherapy; chemo: chemotherapy; - WBHT alone

<sup>\*2</sup> +: vague; +: moderate; ++: severe; +++: disabling pain

<sup>\*3</sup> -: no effect; +: some effect; +: moderate effect; ++: considerable decrease; +++: complete disappearance of pain.

from the WBHT treatment. In 2 cases, pain decrease was considerable, but not complete, for a duration of 4 and 7 months, respectively. In 1 case, there was some decrease in severity of pain for a period of 2 months.

In 6 cases, the pain was vague or at a moderate level before treatment. The palliative effect in these cases was less outspoken. In only 1 case (case 7) the vague pain in the upper abdomen had completely disappeared immediately after WBHT, for a period of 3 weeks. In case 24, the pain originating from his gastric tumour, became less severe, but did not disappear, even not following surgical removal. In the other 4 cases no palliative effect was observed.

#### The occurrence of metastasis following WBHT

In thirteen of the 27 patients no clinical evidence was found for distant metastasis when they were subjected to their first WBHT treatment. Six of them had developed metastasis 2½-29 months after their first WBHT. Six patients died with symptoms of locally progressing tumour only. In one case (no 11) it was not clear whether the malignant mesothelioma nodules in the thoracic wall resulted from metastasis or from local regrowth. The metastasis pattern observed was not uncommon for the specific tumours: twice to the brain (cases 5 and 6, lung adenocarcinoma); three times to the lungs (cases 14, 19 and 23 with sarcomas) and once to the liver (case 24, gastric adenocarcinoma).

#### Survival time

The survival data are presented in figure VI-7.

Only 1 patient (case no 13) is still alive at present, 6 years following her first WBHT treatment.

Four patients died within 1 month following WBHT, of whom two as a consequence of the treatment (cases nos 18 and 27). The remaining 22 patients died 2-44 months following WBHT, all due to tumour progression.

#### Toxicity

##### General Toxicity

Clinical difficulties during the WBHT procedure were encountered in 2 patients. Patient no. 3 developed acidosis with ventricular tachycardia during cooling, which was secondary to insufficient spontaneous ventilation. Administration of bicarbonate solved this problem. In patient no. 26 we were forced to interrupt the WBHT treatment session and start cooling 10 minutes before schedule when the ECG showed periods of asystole. The patient showed no further cardiac problems during and following cooling.

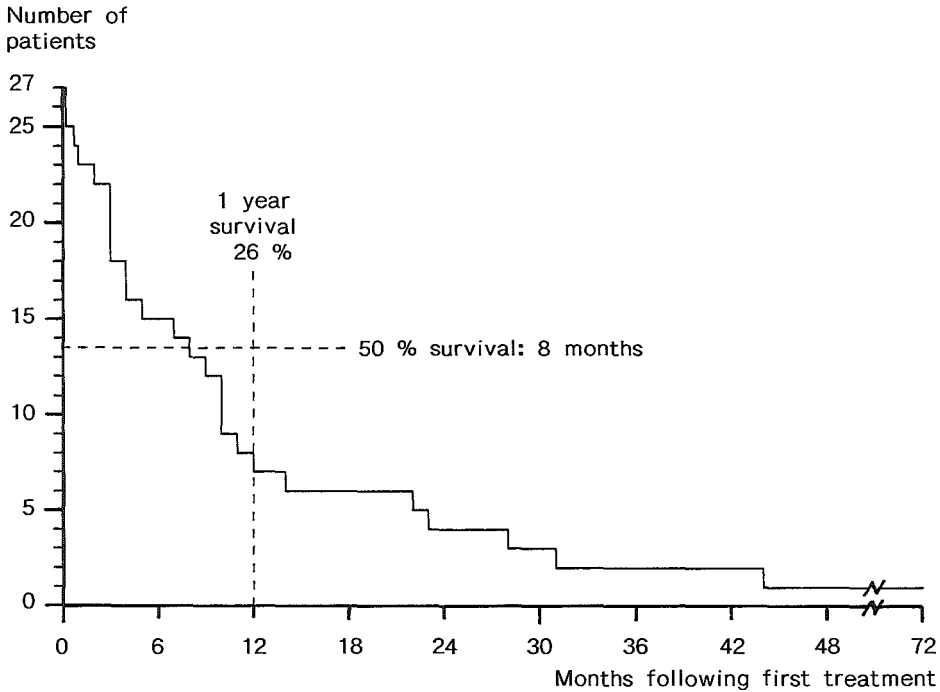


Fig. VI - 7 OVERALL SURVIVAL OF PATIENTS FOLLOWING WBHT TREATMENT

Following cooling, the patients were transferred to the intensive care unit where they remained until the next morning if their general condition allowed transfer to a standard ward. During this period in most patients neurological disorders were observed, in the form of hyperexcitability and agitation. We initially considered that these behavioural changes might be caused by a mild degree of cerebral oedema, but no obvious oedema was ever present on inspection of the optic fundi. Therefore it was inferred that the neurological disorders were probably related to the low  $Mg^{2+}$  serum level (table VI-11). Gastrointestinal disorders such as vomiting and diarrhea were observed in 23 of 27 patients. Decreased levels of potassium ( $K^+$ ) and Ca were corrected by intravenous supplementation. Electrolyte losses in the urine did not fully explain the decrease in serum levels (data are given in table VI-11).

The loss of  $K^+$  may be explained by losses via the sweat and that of the electrolytes  $K^+$ ,  $Mg^{2+}$ ,  $P^-$  and  $Ca^{2+}$  by loss of fluids via vomiting and diarrhea. The composition of these fluids was however not measured. In some patients the hemoglobin level had decreased to such low values ( 6 - 6.5 mmol/l) that



Table VI-11 CHANGES IN RELEVANT MEAN LABORATORY VALUES DURING AND FOLLOWING WBHT

	-24 hr	Mid-plateau	1/4 hr cooling	+ 24 hr	+ 48 hr
<b>Electrolytes</b>					
Na <sup>+</sup> (mmol/l)	139.9	134.5	134.0	137.6	139.6
Cl <sup>-</sup> (mmol/l)	100.9	104.7	102.8	107.9	105.4
K <sup>+</sup> (mmol/l)	4.29	4.61*	3.50*	3.74*	3.72*
total Ca (mmol/l)	2.34	2.02*	2.00*	2.08*	2.14*
free Ca (mmol/l)	1.39	---	1.32	1.30*	1.30*
Mg <sup>2+</sup> (mmol/l)	0.92	---	0.66*	0.69*	0.85*
P <sup>-</sup> (mmol/l)	1.12	0.65*	0.58*	0.91*	0.81*
<b>Haematology</b>					
haemoglobin (mmol/l)	7.8	6.4*	6.5*	6.7*	7.2*
leucocytes (10 <sup>9</sup> /l)	9.0	---	17.2*	9.0	8.8
<b>Coagulation</b>					
< platelets (10 <sup>9</sup> /l)	262	222	127*	89*	100*
fibrinogen (g/l)	4.5	---	2.8*	2.9*	3.9
Glucose (mmol/l)	6.6	8.6*	13.0*	7	5.7
Total protein (g/l)	71	56*	54*	58*	62*
<b>Enzymes</b>					
alk. phosphatase U/l	29.7			31.6	34.3
acid phosphatase U/l	5.71			5.11	5.73
SGOT U/l	12.9			48.4*	210*
SGPT U/l	13.6			27.9*	141*
LDH U/l	157			243*	437*
-iso 5 (liver) (%)	3.9			9.0*	11.6*
CPK U/l	21.7			156*	99*
<b>Kidney functions</b>					
urea (mmol/l)	4.8		6.2	7.2*	5.8*
creatinine (umol/l)	81		142	91.8	87.2
<b>Output in urine (mmol/24 hr)</b>					
		24 hr before WBHT		day of WBHT	
Ca		2.61		2.55	
Na		93		186*	
K		51		89*	
Mg		2.22		1.12	

Remarks: All -24 hr values were within normal range.

\*Significant change with regard to -24 hr values (Student's T-test, 2P<0.05).

transfusion of red blood cells was given.

Patients with no complications could be mobilised from the first day following whole body hyperthermia. Coagulation parameters were found to show evidence of a low-grade disseminated intravascular coagulation in 6 patients, i.e., a decreased fibrinogen level, a decreased number of thrombocytes and an increase in fibrinogen degradation products (FDP) above 20 mg/l, which was maximal 24 hr following WBHT. The partial thromboplastin time was more than doubled in only 3 patients. There was only 1 patient with clinical evidence of coagulation problems following the second WBHT treatment; the puncture in the femoral vein, through which a hepatic vein catheter had been introduced, haemorrhaged for several hours. This patient had, however, no increase in FDP levels.

Some degree of liver damage was observed in most patients. Serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and lactate dehydrogenase (LDH) levels increased significantly, with maximum levels at 48 hr post-treatment. The relevant laboratory values are presented in table VI-11.

Circumoral Herpes simplex infection was observed in 10 of 27 patients following their first WBHT treatment and in 4 of 13 patients following subsequent treatments. In one patient (no. 25), the Herpes infection spread to the eye. This Herpes keratitis could be controlled and did not cause permanent damage. Second degree burns developed in 9 patients; decubitus was seen at the site of the coccyx in 2 patients and on the occiput in 2 others. Burns occurred at pressure sites caused by infusion lines, thermocouple lines or sites where the skin was directly exposed to hot air streams. The risk of developing burns could be reduced by careful insulation and cushioning.

A generally experienced subjective side effect was fatigue, lasting from 1 to 14 days, similar to that following a period of febrile disease.

#### Severe toxicity

Two patients died following treatment. These patients and the treatment procedure will be described here in more detail.

#### Patient no. 18

The pretreatment examinations in this patient had not shown contraindications for WBHT treatment, although there were some abnormalities on the liver scan. The static <sup>99</sup>Tc liver scan revealed a decreased activity at the site of the liver hilus, indicative for a space occupying process. A supplementary

functional  $^{99}\text{Tc}$  scan was performed (HIDA), which showed good functioning of the hepatocytes but a somewhat retarded excretion of bile into an enlarged gall bladder. Laboratory values for liver enzymes were found to be within normal limits, and so the overall functioning of the liver appeared good. The patient was medicated with INH (isonicotinhydrazide), from one week before WBHT treatment in order to prevent flare-up of an old tuberculous process in the lungs by irradiation.

The WBHT treatment was given according to standard procedure. Anaesthesia was maintained by a mixture of 33% oxygen and 66% nitrous oxide, to which 0.5 - 1.5% halothane was added. The body temperature was raised from 37.8 to 41.8°C in 90 minutes. The highest rectal temperature measured was 41.9°C, the hyperthermia dose 2 hours at 41.8°C. Cardiovascular parameters showed "normal" values, i.e. within the range observed during other WBHT treatments, for example during plateau phase: the mean arterial pressure varying from 50 to 80 mmHg, the cardiac output varying from 8 - 12 l/min and the heart rate was maximally 125 beats/min. Total fluid administration was 3 liter in 5½ hours, urine production was reasonably constant with a mean output of 50 ml/hr. Cooling from 41.8 to 39.6°C (rectal temperature) was achieved in 35 minutes. The evening and night following WBHT were uneventful. On the first day following WBHT laboratory values were indicative for disseminated intravascular coagulation. When this had not recovered on the second day (platelet number 29.000/mm<sup>3</sup>, fibrinogen 0.4 gm/L, FDP 40-80 mg/L - pretreatment levels of 230.000, 2.6 and < 20 respectively), treatment with fresh plasma and low dosage of heparin was started. This resulted in improving coagulation parameters. From the second day following WBHT, ever increasing serum levels of liver enzymes (SGOT, SGPT, LDH) and bilirubin were observed, indicating severe liver damage. The patient's condition continued to deteriorate; at 3 days post WBHT the SGOT had risen to 1738 U/L, the SGPT to 2002 U/L and the LDH to 2185 U/L. She became icteric and unconscious and died on the 5th day following WBHT in hepatic coma. Post mortem examination showed that death was caused by massive liver necrosis, with only a few vital hepatocytes left at the periphery of the liver lobules.

#### Patient no. 27

Also in this patient pretreatment examinations had not revealed contraindications for WBHT treatment. His lung function had been remarkably good considering his age (69 years) and considering the tumour localization and extent (mesothelioma over the surface of 1 lung). Vital capacity (VC) was 3400 ml

(93% of normal value) and the forced expiratory volume in 1 second was 72% of VC (54% is the normal value).

Bicycle ergometry was performed up to 120 Watts without evidence of coronary insufficiency, with only minor and acceptable rhythm disorders and with a normal course of blood pressure.

From a few days before hospitalization, one day before WEHT treatment, the patient had become bedridden due to severe pain in the affected part of the thorax.

WEHT was administered following the standard procedure, except for an additional temperature measurement within the liver via the catheter advanced into one of the hepatic veins. Rectal temperature was increased from 37.9 to 41.7°C in 110 minutes. The highest rectal temperature achieved was 42.1°C, the hyperthermia dose was 2 hours at 41.9°C. Cooling from 42.1 to 39.3°C was achieved in 40 minutes. The procedure was uneventful.

In the evening of the day that WEHT had been given, the patient's temperature increased up to 39.6°C, attended with chills. Blood collected at that time for bacteriologic culture appeared sterile. Treatment with antibiotics was started. On the following days, the patient remained feverish and became increasing dyspnoeic. X-ray photographs showed inhomogeneous infiltration of the upper and middle part of the tumour-free lung, which did not worsen much during the following days. The patient however, became that much dyspnoeic that artificial respiration was judged necessary from the second day following WEHT. Despite ventilation with positive end-expiratory pressure and a high percentage of oxygen, and continuing treatment with antibiotics, the patient's condition deteriorated gradually.

Cardiovascular function also became insufficient and the patient died on the 7<sup>th</sup> day following WEHT.

Post mortem examination showed massive oedema of both lungs, with deposition of hyaline fibers within the alveolar membranes and in the alveoli, with beginning of organization. This picture was indicative for adult respiratory distress syndrome (ARDS). The resulting insufficient lung function was judged to have caused death.

Extensive retrospective analysis of both patients yielded no indications in either the previous histories or the pretreatment examinations that could have alerted us to the possibility of these calamities occurring in these patients.

b) Other severe toxicity:

Patient No. 14 experienced considerable liver damage, with a maximum SGOT of 1380 U/l (norm < 19 U/l) and clinical jaundice, but recovered from the third day. Three other patients (Nos 12, 13, 21) had SGOT levels > 300 U/l but no clinical symptoms. Two patients, Nos 9 and 26, were seriously dyspnoeic immediately after WBHT and had to be artificially ventilated for 12-36 hr. Both of these patients suffered from carcinomatous lymphangitis of the lungs and had impaired ventilation before hyperthermia.

Two patients, Nos 1 and 3, developed third-degree burns during WBHT. In the first patient this could be attributed to the additional local tumour heating with microwaves during anaesthesia, which probably as a result of "standing waves" combined with circulation stoppage caused an unobserved hot spot. Patient No. 3 had burns on his toes, probably due to poor regional circulation and an excessively high local temperature in the exposed skin.

Patient no. 21 appeared to have brain metastasis following treatment. This was suspected when he developed a hemiparesis 48 hr after WBHT. CT scanning showed multiple oedematous brain metastases. Brain scanning had not been included in

Table VI-12 INDOCYANINE GREEN-CONTINUOUS INFUSION DATA.

$T_{\frac{1}{2}}$  is the plasma half-life of ICG at the start of heating (s.h.). The clearance values and arterial concentrations of ICG showed no trends with time and are thus expressed as mean concentrations  $\pm$  SD. Liver damage following treatment is expressed as maximum serum transaminase (SGOT), the normal range being up to 19 U. l<sup>-1</sup>

Patient, treatment	$t_{\frac{1}{2}}$ at s.h. (min)	Arterial concentration (mg.l <sup>-1</sup> )	Infusion rate (mg.min <sup>-1</sup> )	Clearance (l.min <sup>-1</sup> )	SGOT max (U.l <sup>-1</sup> )
20-1	5.04	0.52±0.07 <sup>a</sup>	0.167	0.47±0.08 <sup>a</sup>	18
21	2.29	0.48±0.01	0.333	1.02±0.01	336
22	3.96	0.67±0.06	0.333	0.73±0.07	72
20-2	2.06	0.29±0.09	0.333	1.80±0.69	29

<sup>a</sup> Mean  $\pm$  SD

the pretreatment examinations of this patient, as we erroneously assumed that the likelihood of the presence of brain metastasis from a pleural mesothelioma was negligible. Corticosteroid therapy and subsequent radiotherapy of the brain gave however a rapid recovery.

Hepatic clearance of ICG

During WBHT

The use of the Fick principle to estimate hepatic blood flow (HBF) requires the attainment of a stable arterial concentration of ICG. The assumption can then be made that dye removal by the liver is equal to input by infusion. Over the infusion period (5-6 h per patient), arterial dye concentrations were relatively stable (see table VI-12). From these and the hepatic venous concentrations, the extraction ratios were calculated.

In all four patients, the extraction ratio decreased once the patient was at a

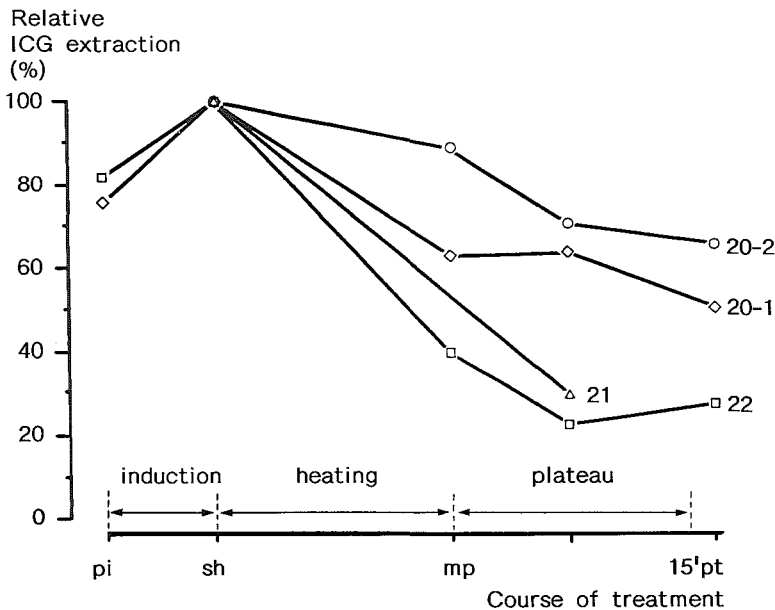


Fig. VI - 8 ICG EXTRACTION DURING WBHT

Changes in indocyanine green (ICG) extraction during WBHT. The graph shows the changes in ICG extraction (E) relative to E at the start of heating (sh) during four WBHT treatments. Patient number and treatment number are indicated with the curves.

core temperature of  $41.8^{\circ}\text{C}$  (see figure VI-8). All three patients with post-treatment measurements also showed a considerable decrease as compared with prewarming values. The increase in extraction seen at "start heating" in the two patients with preinduction values correlates with the (expected) decrease in hepatic blood flow (see table VI-13) following induction of anaesthesia. The values obtained for estimated hepatic blood flow (EHBf) before the induction of anaesthesia and at "start heating" represent about 35% of the cardiac output (CO) but once heating had started these values increased greatly, in two cases they were found to amount to more than 50% of the CO. During treatment, the variation in flow values also increased. The patient suffering the greatest post-treatment liver damage (patient 21; see table

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Table VI-13 A COMPARISON OF ESTIMATED HEPATIC BLOOD FLOW (EHBf) AND CARDIAC OUTPUT (CO) DURING WHBT.

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EHBf and CO are expressed in  $\text{l min}^{-1}$ . CO was measured by thermodilution using a Swan-Ganz catheter.

Patient, treatment	Point in treatment									
	p.i.		s.h.		s.p.		m.p.		15' p.t.	
	EHBf	CO	EHBf	CO	EHBf	CO	EHBf	CO	EHBf	CO
20-1	2.30	6.1	1.35	4.7	1.96	10.5	2.58	12.0	2.47	9.5
21			2.25	6.0			7.64	13.4		
22	2.18	6.1	1.38	4.5	4.02	12.0	6.89	14.1	5.22	12.1
20-2			1.88	4.9	3.41	10.2	5.90	11.3	3.05	10.8
mean	2.24	6.1	1.72	5.0	3.13	10.9	5.75	12.7	3.58	10.8
SD	0.08	0	0.43	0.67	1.06	0.96	2.23	1.28	1.45	1.30

---

p.i.: pre-induction of anaesthesia

s.h.: start heating

s.p.: start plateau

m.p.: mid plateau

15' p.t.: 15 minutes after start cooling

---

VI-12), as evidenced by serum transaminase (SGOT) elevation, was also the one in whom the highest flow value was estimated at midplateau, and in whom the lowest hepatic vein oxygen saturation values were measured after reaching plateau (see figure VI-9).

Once cooling had been initiated, the estimated flow values were found to decrease to varying extents and flow expressed as a percentage of the CO returned to normal values (mean = 33% of the CO). Extraction ratios remained low.

Following WBHT

Analysis of the plasma disappearance of ICG following WBHT (after cessation of continuous infusion) revealed an initial rapid phase and, at lower ICG

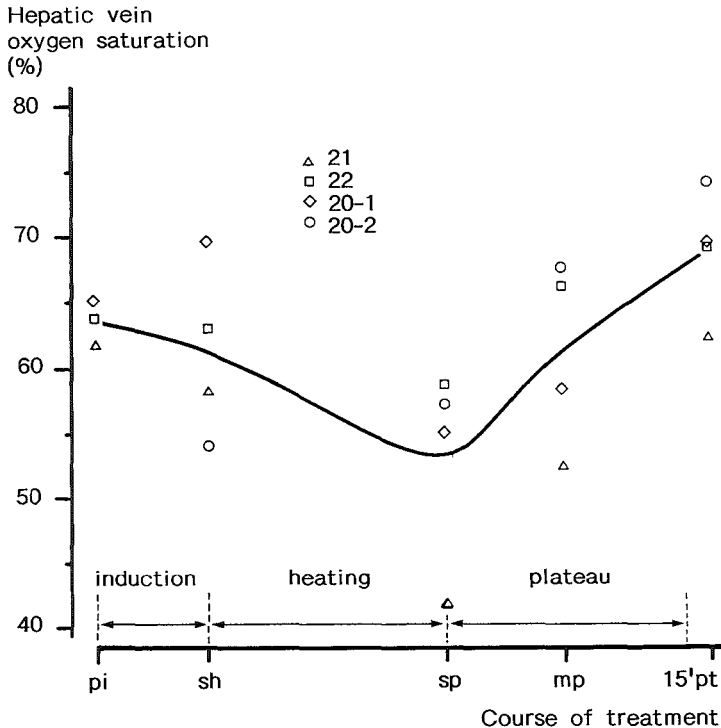


Fig. VI - 9 HEPATIC VEIN OXYGEN SATURATION DURING WBHT

The oxygen saturation of blood in the hepatic vein at various times during four WBHT treatments is shown. The solid line represents the mean. Patient numbers and treatment numbers are given in the figure.



concentrations, a slower disappearance rate (see figure VI-10). It can be seen that a 50% reduction occurred only after about 104 min., although all patients had normal plasma half lives (2-5 min.) before heating (see table VI-12).

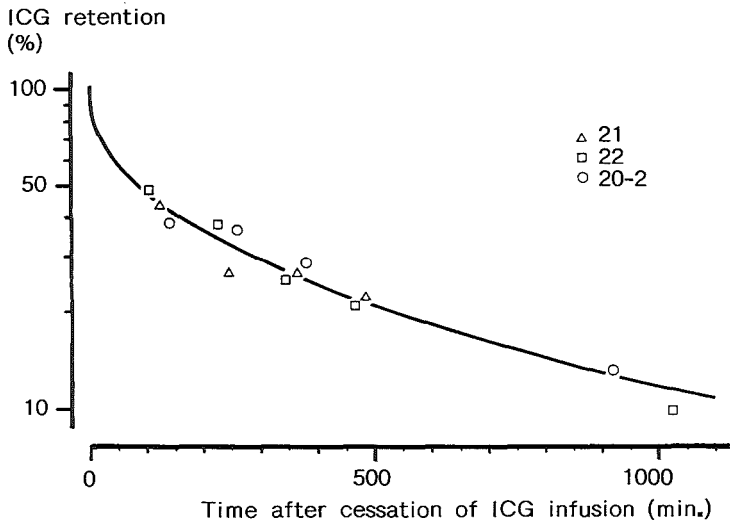


Fig. VI - 10 ICG PLASMA DISAPPEARANCE FOLLOWING WBHT

The plasma disappearance of ICG following WBHT is shown as a percentage of the arterial concentration determined at the termination of ICG infusion. Data fitted with the Weibull distribution (Weibull 1951), a statistical distribution which can be applied to processes with exponential segments (Campos 1975). Patient numbers (and for patient no. 20 the treatment number) are given in the figure.

Cost and benefit

The overall result of the treatment has to be judged for each individual patient. An attempt to weigh profit for each patient, following 30 separately assessable treatments, is represented in table VI-15.

The results which were judged positive and negative, respectively, are given in table VI-14.

The (combined) treatment was considered worthwhile when there were none or only minor complications of the WBHT treatment and when at least one of the responses listed as positive in table VI-14 was achieved. It was considered further that the patient had no benefit when the patient's survival following treatment was less than 2 months.

The final overall results of the estimation for profit score, listed in table

Table VI-14 POSITIVE AND NEGATIVE RESULTS FOLLOWING WBHT

positive	negative
"no change" $\geq$ 2 months	survival $<$ 2 months
"partial response" $\geq$ 2 months	complications following WBHT
"complete response" $\geq$ 2 months	varying from
inoperable $\rightarrow$ operable	- 0 (no complications)
palliation $\geq$ 2 months	- minor-moderate-severe (depending on how much the patient had suffered from the complication)
	- death

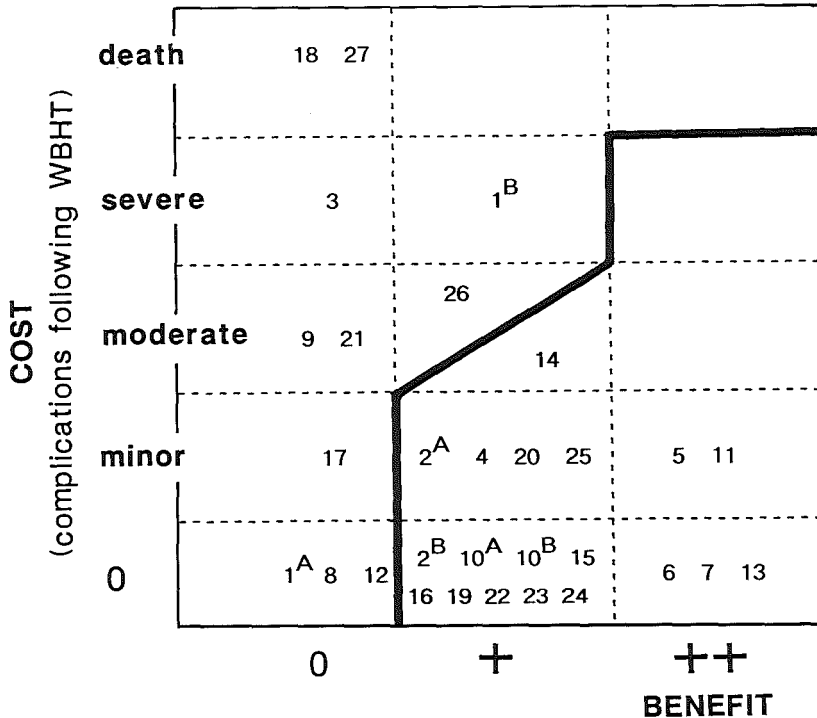


Fig. VI - II COST AND PROFIT "BALANCE"

A schematic representation of the cost and benefit for each individual patient (indicated by patient number) following treatment with WBHT, either given alone or in combination with radiotherapy or chemotherapy. The solid line indicates the division between "positive" and "negative" overall result of the treatment.

Table VI-15 PROFIT SCORE

Patient no	treatment	POSITIVE		NEGATIVE	profit score
		tumour response *1)	palliation *1)	toxicity	
1a	H	progression	-	-	- *2
-b	H + C	NC 3 m	-	severe 3rd degree burn	-
2a	H	NC 3 w	+ 2 m	non-disabling burns of toes	(+)*3
-b	H + C	NC 2 m		-	+
3	H	NC 3 w		disabling burns of toes	-
4	H + R	NC 2(+)m PR 2(+)m		atropin toxicity ?	(+)
5	H + R	CR 10(+)m		lung embolia ?	+ *4
6	H + R	CR 11(+)m		-	+
7	H + R	PR 12 m	+++ 3 w	-	+
8	H + R	PR 1 m	+++ 3 w	-	-
9	H + R	complete regression (autopsy)	+++ 3(+ )w	respiratory problems	-
10a	H + R	PR 3 m	+++ 2 m	-	+
-b	H + C	NC 6 m	+ 6 m	-	+
11	H + R	CR 21 m		atrial fibrillation	+
12	H + R	NC 1 m		-	-
13	H + R + miso	CR 72(+)m		-	+
14	H + R	PR 3 m	+++ 3 m	liver damage	(+)
15	H + R	NC 2 m	+ 2 m	-	(+)
16	H + C	PR 2 m	-	-	(+)
17	H + C	NC 1 m		respiratory problems	-
18	H + R	NE		death (liver necrosis)	-
19	H + R	inoperable - operable	+++ 2(+)m	-	+
20	H + R	NC 7 m	-	2nd degree burns	+
21	H + R	progression	+++ 1(+)m	evidence of brain metast.	-
22	H + R	NC 5 m / 6 m	++ 4 m	-	+
23	H + R	NC 9 m	++ 7 m	-	+
24	H + R	inoperable - operable	+ 24 m	-	+
25	H + R	NC 4 m		Herpes simplex spreading to the eye	(+)
26	H + R	NC 2 m		respiration problems	-
27	H + R	NE	+++ 1(+)w	death (ARDS)	-

The abbreviations used in this table are:

H = whole body hyperthermia; C = chemotherapy; R = radiotherapy; NC = "no change"; CR = "complete response"; PR = "partial response"; NE = not evaluable.

\*1 including duration in months (m) or weeks (w); -, +, ++, +++: see table 10

\*2 negative \*3 weakly positive \*4 positive

VI-15 and schematically presented in figure VI-11, are that WBHT, either given alone or in combination with radiotherapy or chemotherapy, had resulted in

- a weakly to clearly positive effect following 19 treatments;
- a negative effect following 11 treatments.

# DISCUSSION

## Chapter VII

### Efficiency of heating technique

#### Heating rate.

The highest mean heating rate of  $2.7^{\circ}\text{C/hr}$  (range 2 - 3.6) which was achieved by us was achieved with method 3. This value is within the range published by other authors using techniques of transcutaneous energy input (see table VII-1). Pettigrew et al. (1974A) (heating with wax) report to achieve a heating rate of  $3-6^{\circ}\text{C}$  per hour by using an epidural block which induces vasodilatation. Vasodilation in the skin increases the heat conductance and by this way increases the energy transport through the skin into the body.

Blair and Levin (1978) who also used wax for energy transfer found a considerably lower heating rate of  $1.7$  to  $3.1^{\circ}\text{C/hr}$ , the highest value was found when an epidural block was given. The major difference between the two techniques used is that Pettigrew covered the patient with molten wax in immediate contact with the skin, whereas Blair and Levin used wax in bags which made the method cleaner but also may have resulted in an isolating layer between the wax and the skin of the patient.

For the methods using water-perfused blankets or suits, heating rates of  $1-3.3^{\circ}\text{C/hr}$  are published, the mean of all values being  $2.29^{\circ}\text{C/hr}$  (s.d. 0.73).

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Table VII-1 COMPARISON OF EFFICIENCY OF HEATING TECHNIQUES

<u>non-invasive techniques</u>	<u>heating rate (°C/hr)</u>
- wax	
Pettigrew et al. (1974A)	3 - 6
Blair and Levin (1978)	1.7 - 3.1
- water-perfused blankets	
Larkin et al. (1977)	2.5 - 3.3
Barlogie et al. (1979)	1.9
Moricca et al. (1979)	1.6 - 2.5
Bull et al. (1979)	2.5 - 3.3
Herman et al. (1982)	1.8
- water-perfused suit	
Gerad et al. (1984)	1 - 2.5
- water bath	
Versteegh (1980)	6 - 10
- infrared	
Robins et al. (1984)	4.8
- hot air and RF	
Engelhard et al. (1982)	3.5 - 5.3
present study (method 3)	2 - 3.6
 <u>invasive techniques</u>	
- femoral AV shunt	
Parks et al. (1979)	13.4
Lange et al. (1983)	2.5 - 4.9
Herman et al. (1982)	3.8

---

As these methods include isolation of the skin and heating via the front and the back of the patient, these are comparable to our method 3. An important advantage of our method is that the patient is constantly under visual control, and that monitoring lines can be placed easily and without causing pressure points.

Versteegh (1980) found a mean heating rate of  $7.3^{\circ}\text{C}/\text{hr}$  using water-bath heating in 4 patients, who received 10 treatments.

The combination of hot air with radiofrequency as used by Engelhardt et al. (1982) results in a higher heating rate ( $3.5\text{--}5.3^{\circ}\text{C}/\text{hour}$ ), but has the disadvantages of disturbance of electronic monitoring systems and the risk of developing burns where sweat accumulates. Considerably higher heating rates than those generally found with non-invasive methods were reported by the users of heating by femoral arteriovenous shunts. Parks et al. (1979) even report a heating rate of  $13.4^{\circ}\text{C}/\text{hr}$  (a temperature of  $41.8^{\circ}\text{C}$  was reached in only 22 minutes), but this finding is relativized by the heating rates reported by Lange et al. (1983) and Herman et al. (1982), being  $2.5\text{--}4.4$  and  $3.8^{\circ}\text{C}/\text{hour}$ , respectively. The major disadvantage of the invasive technique is that surgery is required before heating sessions can start.

The conclusion can be made that the Rotterdam method for WBHT induction in its final form (method 3) is clinically useful. The time necessary to raise the rectal temperature to  $41.5^{\circ}\text{C}$  is comparable to the time mentioned by most other authors using non-invasive techniques. The plateau temperature of  $41.8\text{--}42^{\circ}\text{C}$  could be well controlled by adjusting the air and water temperatures.

#### Heat dose

The heat dose achieved in most patients was 2 hours at  $41.8^{\circ}\text{C}$ . This heat dose was proven to be efficient to kill part of the tumour cell population as inferred from the observation that some tumour regression took place in those patients treated with WBHT alone (cases 2 and 3). This effect, however, did not result in much benefit to the patients: the regression was minor and short-lasting.

The time to reach  $41.5^{\circ}\text{C}$  varied from 70–230 minutes and may have influenced the biological effect through the induction of thermotolerance. This phenomenon, however, is not quite well understood nowadays. Although in the patients treated with method I and II the heating phase was considerably longer than in the patients treated with method III, the results in the latter group (5 objective responses in 16 cases) were not better than those in the first group (5 objective responses in 10 cases). Herman et al. (1982) also compared the

results of WBHT with various duration of heating phase. Temperature increase to 42°C was accomplished in on the average 2.8 hrs when heating blankets were used (6 patients, 16 treatments) and in 1.3 hrs with the extracorporeal heating method (5 patients, 14 treatments). They also could not demonstrate improved results with faster heating rates. As thermotolerance is not detectable under these conditions, the duration of heating phase is probably not very important when WBHT is used for tumour heating.

The heat dose to the tumour may be different from that delivered to the whole patient when the tumour is located superficially. In fact, we measured tumour temperatures at less than 1 cm depth which were up to 1.1°C lower than rectal temperatures during plateau phase in the group of patients treated without plastic foil (fig. VI-1A). During the heating phase, however, tumour temperature was higher than rectal temperature in this situation (fig. VI-2A). Above 40°C, where hyperthermia becomes effective, this difference was maximally 0.5°C, but the duration of this profitable difference was only 70 minutes and therefore considered insufficient for compensation of the opposite situation during plateau phase.

The situation was improved when plastic foil was used. During the heating phase the tumour temperature was higher than rectal temperature (fig. VI-2B,C) whereas no difference was observed during plateau phase (fig. VI-1B,C). The use of plastic foil thus also adds to the therapeutic value of WBHT for tumours located superficially.

#### Temperature distribution

With the use of plastic foil a rather homogeneous temperature distribution through all tissues was achieved. Most authors report only the measurement of core (rectal, oesophageal, bladder) temperatures during WBHT. Searching through literature on human WBHT, we found only Barlogie et al. (1979) and Robins et al. (1985) mentioning skin temperatures. With the use of water-perfused blankets, skin temperature was close to rectal and oesophageal temperatures during the heating phase, but became considerably below those temperatures after lowering of perfused water temperature for the maintenance of core temperature at 41.9-42.0°C during plateau phase (Barlogie et al. 1979). This pattern is somewhat different from the radiant heat method. Here skin temperature is up to 2°C higher during the heating phase, but 0.4-0.8°C lower than core temperature during plateau phase (Robins et al. 1985). These differences can become critical for superficially located tumours, especially when WBHT is combined with chemotherapy, since usually the drug is admin-



istered at the start of plateau phase.

The use of radiofrequency or microwave heating may result in higher local temperatures (present study: dog experiments (chapter IV) and patient 1 (chapter VI)), which is advantageous when the tumour is located in that particular area, but we found the disturbance of the electronic read-out parts of the monitoring equipment too disadvantageous and the risk of severe burning too high to use these parts of the original Pomp-Siemens cabin.

More information about temperature distribution during WBHT is given in reports on animal experiments. Temperature distribution during WBHT in pigs, induced by humidified heated air, is described by Dickson et al. (1979). Subcutis, muscle and bone marrow temperatures were consistently lower than rectal temperature at normothermia and during hyperthermia. Kidney temperature was similar to that found for rectum and oesophagus, which were close together. The highest brain temperature was about equal to rectum temperature but the side on which the animal lay almost invariably maintained a temperature difference of  $+0.3 - +0.5^{\circ}\text{C}$  above the other side (Dickson et al. 1979). We observed similar, although insignificant differences in our experiments with dogs: one side of the brain was  $+0.1 - +0.2^{\circ}\text{C}$  higher in temperature than the other side. This difference may be explained by the cooling mechanism: venous blood draining from the skin of the head into the cranium is cooler than core temperature and thus functions as a heat exchanger. The same mechanism may play a role in human subjects (Truex and Carpenter 1969).

Liver temperature, in Dickson's experiments, was at "start heating" somewhat ( $+0.4 - +0.2^{\circ}\text{C}$ ) higher than rectal and oesophageal temperature, respectively, but the difference became less with increasing time at hyperthermia. This finding agrees partially with the only measurement of liver temperature in our patient series, where a difference with rectal temperature of maximum  $1.0^{\circ}\text{C}$  was observed during the heating phase, which difference was reduced to zero after 40 minutes at plateau temperature.

Robins et al. (1983), heating pigs with the radiant heat method, find a liver temperature-time pattern which is "qualitatively similar to that found for rectum". Another experiment in which liver temperature is reported (Macy et al. 1985) indicates a liver temperature  $0.3^{\circ}\text{C}$  lower than rectum temperature, during plateau phase. This was found during heating of dogs using humidified heated air. We have no explanation for this different finding.

## Tumour pH

Tumour pH was considerably lower than arterial pH in 4 of 7 paired determinations. During plateau phase we observed no changes in tumour pH. The measurement during heating phase was considered unreliable, as experience with tumour pH determinations in other, unanaesthetized, patients has learned that, following introduction of the electrode, a recovery phase of 50-90 minutes is required before stabilization (of the physiological status) is achieved. (Wike-Hooley et al. 1985).

This absence of change in pH may be a matter of temperature. Vaupel et al. (1983) suggest that hyperthermia-induced changes in tumour pH occur only at temperatures of 43°C and higher and, indeed, Song et al. (1980B), Bicher et al. (1980) and Vaupel (1982), who observed pH changes, all used temperatures of 43°C or more. Experiments on Yoshida sarcoma at 42°C showed no change in pH (Dickson and Calderwood 1979), although changes were seen in this tumour following hyperthermia at 44°C for 60 minutes.

For the increased tumour pH value in patient 10, 2 weeks following his first WBHT treatment within a series of radiotherapy, two explanations are available. Following his first WBHT, the tumour has regressed excessively. The increase of pH may reflect either a "normalization" of tumour tissue, i.e., an improved blood flow, or the opposite: necrosis. A shift in tumour pH to more alkaline values with tumour necrosis has been demonstrated in experimental studies. For example Busse et al. (1981), who investigated DS sarcoma in rats, found that when tumours were very necrotic, the pH increased with increasing size - rising from 7.2 to 7.4 as tumours increased from 1.7 to 25.7 g. Vaupel et al. (1981) have also found alkaline values in very necrotic CH3 mouse mammary adenocarcinomas.

In another group of patients in whom tumour pH was measured before and after a series of radiotherapy combined with local hyperthermia, a highly significant increase in tumour pH was seen (Wike-Hooley et al. 1984A). This rise in pH is probably a result of improved oxygenation and blood circulation. Such changes in oxygenation have been reported following clinical radiotherapy only, for example by Mäntylä et al. (1982) and Pappova et al. (1982).

As we did not perform histological studies of the tumour, both explanations are plausible. Patient 10 was referred for a third treatment two months after the second, when the tumour was progressing again. By that time tumour pH had reached a very acidic level.

In patient 15, tumour pH values showed only a minor change 1 week after the first WBHT treatment. The tumour size had hardly changed by that time.

In view of the fact that we did not observe a decrease in tumour pH during WBHT, no additional therapeutic effect through this mechanism can be expected during the treatment with the method used by us.

The subcutaneous pH was found to be higher than tumour pH in the two paired measurements performed during WBHT. This is in accordance with the findings in unanaesthetized patients, where a mean difference between subcutaneous and tumour pH of 0.34 was found (Van den Berg et al. 1982).

### Tumour response

Our tumour response data fit well in those reported by other investigators. In table VII-2, the results obtained and published are summarized.

Following WBHT alone "complete response" was never achieved by these authors, including the present study. "Partial response" was observed in 0-49%, overall 32% of the patients. In the present study, some regression was observed in two cases (no. 2 and 3) and no change in two other cases (4 and 12). The rapid partial regression observed in patient no. 2, in whom vascular stasis in the tumour was visible already during the first WBHT session, resembles the circulation stoppage and central necrosis as was demonstrated by Reinhold et al. (1978) in experimental tumours. The "no change" effect in cases 3, 4 and 12 can be interpreted as a certain amount of cell kill in the poorly perfused parts of their tumour, rapidly overgrown by proliferation of the undamaged cells in the well perfused areas.

This agrees with the findings of experimental studies: a hyperthermia dose of 2-4 hrs at 41.5 to 42.2°C may be sufficient to kill tumour cells in a thermo-sensitizing environment including hypoxia and low pH but not the more heat-resistant cells at the, well perfused, tumour margins. However, two cases in whom "complete response" was (almost?) obtained following WBHT alone were reported by Warren (1935) and Wüst (1975). Warren describes how all visible tumour nodules in a patient with metastasized hypernephroma had disappeared over a period of 5 months following 3 WBHT treatments of 5 hrs at 41.5°C. At that time regrowth of brain metastases had occurred. Wüst reports on a complete remission of 5 months duration obtained in a, previously not treated (!), patient with Hodgkin's disease, following 12 WBHT treatments of 1 hr at 40°C. The results in 11 other patients were not that impressive, and he suggested that higher treatment temperatures would be necessary.

Following WBHT combined with chemotherapy, we found no "complete response" either and only 1 of 5 patients showed a "partial response". Other inves-

Table VII-2 TUMOUR RESPONSE FOLLOWING WBHT

	<u>WBHT alone</u>			<u>WBHT + chemotherapy</u>			<u>WBHT + radiotherapy</u>		
	<u>CR</u>	<u>response</u>	<u>pain relief</u>	<u>CR</u>	<u>response</u>	<u>pain relief</u>	<u>CR</u>	<u>response</u>	<u>pain relief</u>
Pettigrew et al. 1975		22/49	24/49		12/15	10/15		3/3	3/3
Priesching 1976					6/16				
Levin and Blair 1978							1/14	8/14	++
Parks et al. 1979				3/25	13/25	25/25			
Moricca et al. 1979				0/15	1/15	11/15			
Bull et al. 1979	0/13	1/13							
Barlogie et al. 1979	0/5	0/5		0/6	0/6				
Herman et al. 1982				0/10	6/10				
Engelhardt et al. 1982				8/15	13/15				
Lange et al. 1983				0/13	1/13				
Koga et al. 1985				0/13	3/13				
Hinkelbein et al. 1981				2/11	4/11		2/9	4/9	
present study	0/6	0/6	2/3	0/5	1/5	1/3	4/17	8/17	11/12
Overall	0/24	23/73	26/52	13/113	60/144	47/58	7/40	23/43	14/15
%	0	32	50	12	42	81	18	53	93

tigators report "complete response" percentages varying from 0 to 53. The highest "complete response" rate (53%) was reported by Engelhardt et al. (1982), combining WBHT (1 hr, 40.5°C) with multidrug therapy (adriamycin, cyclophosphamide and oncovin (ACO)), in treating 15 patients with oat cell carcinoma of the lung. The 50% survival time in these patients was 12.3 months, which means a prolongation of 4.7 months in comparison with a historical control group treated with ACO under normothermic conditions.

As most investigators have used reduced drug dosages when administered during WBHT, the therapeutic possibilities of the combination WBHT and chemotherapy may be underestimated at the time. For the time being, however, insufficient data are available on the increased toxicity of chemotherapy under hyperthermic conditions. It is unlikely that the simultaneous combination will be without increased toxicity. It is possible that the results of further experimental investigation will indicate ways to improve treatment of patients with metastatized tumours with the combination of WBHT and chemotherapy. Therapeutic gain can be expected when the two treatment modalities with different mechanisms of action are administered additionally, e.g. with a time interval long enough to exclude the possibility of enhancing or resistance-inducing effects of hyperthermia on chemotherapy. In this case hyperthermia will kill the cells in the poorly perfused areas of the tumour whereas the drug(s) should attack cells in the well perfused areas.

The combination of WBHT and radiotherapy results in the highest response percentages: in the present study the "complete response" rate is 24%, the overall "complete response" rate is 18%, and response is obtained in about half of the patients. Responses and even "complete response" have been obtained using radiation dosages as low as 24 Gy or less (present study). The effect of WBHT in this combination, however, is only an enhancement of local radiotherapy efficacy. For the patient's benefit (see chapter VI, "Toxicity") the combination of radiotherapy with local hyperthermia is therefore preferable. There are, however, many problems in inducing local hyperthermia in deep seated tumours which have not yet been solved.

We once obtained the impression that previously irradiated tumours responded better to WBHT and radiotherapy than previously non-irradiated tumours. This was especially the case in patients with intestinal tumours. Patients no's 8 and 10 both showed partial response following WBHT and low dosages of radiotherapy on a tumour which had recurred after previous radiotherapy, whereas the primary treatment of patient no. 20 with WBHT and a high dose of radiotherapy resulted only in "no change" for a duration of 7 months. The remark-

able complete regression however of the previously not irradiated pelvic metastasis of breast carcinoma in patient no. 9 does not fit in this impression, just like the observation in patient no. 4. In patient no. 4 the previously irradiated melanoma lymphnode metastasis showed "no change" following WBHT and 30 Gy whereas the previously non-irradiated metastasis showed "partial response". The explanation for these contradictory observations is probably that tumours respond differently depending on various specific characteristics such as, for example, histology and physiology.

Pain relief following WBHT treatment has been observed not only by us but by many authors, whether WBHT is given alone or in combination with radiotherapy or chemotherapy. The percentage of patients experiencing pain relief reported is the highest in the combination with radiotherapy group: 92-100%. Some authors mention that pain disappeared immediately following treatment, even in patients in whom the tumour failed to respond (Levin and Blair 1978, Parks 1979, Pettigrew et al. 1974B). In our series, this was the case with patient no. 23. The, previously present, paresis of one leg, due to compression on the corresponding nerve root by the tumour, transiently aggravated following WBHT, which was probably caused by oedema in the tumour. Yet in contrast to the aggravation of this symptom, the immediate pain relief was remarkable in this patient.

It has been suggested that the increase in Bèta endorphin blood levels, which was observed to be induced by WBHT (Robins, personal communication), might be responsible for this palliative effect. Bèta endorphin is released by the pituitary gland under conditions of stress and has a strong analgetic action. Whatever the cause, for the patients this effect of pain relief means a worthwhile improvement of quality of life.

## Toxicity

### General Toxicity

Toxicity following WBHT does not only depend on heat dose administered during treatment, but on other factors as well, such as:

- the general condition of the patient; the condition of his organ systems (heart, lungs, liver, kidney, haematology);
- physiologic conditions during treatment, which may be influenced by anaesthesia measures, artificial respiration, infusion schedule, heating rate;
- combination with (prior) chemotherapy or (prior) radiotherapy;

- post-hyperthermia care;
- tumour necrosis.

The heat dose administered during WBHT is important with regard to toxicity, as illustrated by the experience of investigators who treat patients with "moderate" WBHT. Below a treatment temperature of  $41^{\circ}\text{C}$ , toxicity is minimal. The group in Freiburg experienced cardiac problems during WBHT in two patients. A 68-year-old patient developed left ventricular decompensation during her 13th WBHT, which was controlled without further problems (Hinkelbein et al. 1981). In another patient, cardiac arrhythmia was observed during WBHT which necessitated termination of treatment. This complication was probably due to enhancement of the cardiotoxicity induced by Adriamycin, as the patient had received a cumulative dose of 620 mg (Neumann et al. 1982). Normal rhythm returned when the patient was cooled to normothermia.

Other side effects include 2nd degree burns (Wallach et al. 1982), Herpes simplex (Heckel and Heckel 1979) and neuropathy (Neumann et al. 1979). Laboratory data for haematology and electrolyte blood levels did not show significant changes during and following WBHT at this low temperature and there were no indications for liver or kidney damage.

With treatment temperatures above  $41^{\circ}\text{C}$ , toxicity was much more marked. In our series, few problems were encountered during the treatment. In patient no. 3 the cardiac arrhythmia during cooling was due to acidosis caused by respiratory insufficiency. This could be prevented in subsequent patients by artificial ventilation. The cardiac arrhythmia in patient no. 26 was unexpected but appeared to be rapidly reversible by cooling. Other authors also report the necessity of termination of treatment due to cardiac arrhythmia or circulation failure in several cases (Larkin et al. 1977, Priesching 1976). Hypotension during and following WBHT was a commonly observed phenomenon. Though in cases where the cardiac output was measured there was not usually any indication of decreased whole-body oxygen flux (Faithfull 1983). The problems during the first few hours following WBHT were the same as observed by many other authors (Pettigrew et al. 1974A, Mackenzie et al. 1975, Priesching 1976, Larkin et al. 1977, Barlogie et al. 1979, Bull et al. 1979, Moricca et al. 1979, Herman et al. 1982, Gerad et al. 1984).

Gastrointestinal disturbances such as diarrhoe and vomiting were sequels to almost every treatment, indicative for damage to the intestinal mucosa.

Decreased levels of  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$  and  $\text{P}^-$  were found following every treatment. During WBHT an increase in potassium level was observed, followed by decreased levels in the post-treatment phase. In most cases only  $\text{K}^+$  and  $\text{Ca}^{2+}$

were corrected for by intravenous administration. In general, normal levels were again reached by 72 hours following WBHT. The decrease in total serum calcium gave no clinical sequelae, as the ionized calcium remained within normal limits. The decreased total calcium concentration probably resulted from the decrease in total protein concentration. Transient hyperexcitability and agitation were seen in 19 patients following 23 WBHT treatments and were, retrospectively, probably the result of a magnesium deficiency. It was necessary to administer diazepam to 12 patients to subdue them. Other than this restlessness and the clinical manifestation of brain metastasis in patient no. 21, we found no neurological disorders.

Other authors report peripheral nervous system problems in the form of neuropathy, in some cases probably due to "recall" Vinca-toxicity (Barlogie et al. 1979, Bull et al. 1979), and acute myelopathy, probably due to synergism of prior radiotherapy and hyperthermia combined with chemotherapy (Douglas et al. 1981). Complications concerning the central nervous system such as epileptic insults, brain oedema and haemorrhage and oedema from brain metastasis have also been reported (Priesching 1976, Barlogie et al. 1979, Herman et al. 1982, Gerad et al. 1984). Kidney function changes are generally not a problem; during treatment oliguria may occur, but diuresis recovers soon after cooling. Decreases in the concentration of haemoglobin were seen by Pettigrew et al. (1974A), and in our patients significant falls were seen during warming and also at the onset of cooling. These changes were almost certainly at least partly due to haemodilution consequent upon vasodilatation and net movement of fluid into the vascular space. This view is also held by Larkin et al. (1977). The Hb values in our patients remained significantly lowered till 48 hours after the commencement of cooling.

Many authors report a leucocytosis following WBHT. Pettigrew et al. (1974A) reported a mean rise of 67% in white cell counts following 4 hours WBHT, returning to normal with 24 hours. There would appear to be an absolute rise in the polymorphonuclear cells accompanied by decrease of lymphocytes. In our patients, total white cell counts were significantly raised for up to 4 hours after cooling commenced and lymphocyte counts were depressed for 3 days following WBHT.

Disseminated intravascular coagulation (DIC) was observed by Pettigrew et al. (1974B), who described 4 patients who died following WBHT with evidence of DIC. Barlogie et al. (1979) also reported prolongation of the prothrombin and partial thromboplastin times with mild to moderate decrease of fibrinogen levels and increases in fibrin degradation products (FDP). Although we did



indeed find a decrease in the number of platelets and in the fibrinogen levels following every WBHT treatment, these were accompanied by an increase in FDP above 20 mg/l in only 6 and above 40 mg/l in only 3 of 45 treatments. The only patient with clinical coagulation problems had no elevation of FDP, although the combination of bleeding and the changes in levels of coagulation parameters made the diagnosis DIC probable.

Some degree of liver damage occurred in most of our patients, as judged from the increase in liver enzyme serum levels. Impairment of liver function is a frequently observed sequel of WBHT treatment. As liver damage caused the death of one of our patients, this complication is separately discussed below.

Respiratory problems following WBHT occurred in two patients (nos 9 and 26) with carcinomatous lymphangitis of the lungs; they had to be artificially ventilated for 24 hours. Oedema of the tumour metastases -diffusely spread over both lungs-, resulting in increased obstruction of the airway, had probably occurred. Patient no. 27 died as a result of adult respiratory distress syndrome, which complication is discussed below.

Sites of decubitus developed in patients nos. 7,8 10 and 11. At pressure sites, hypoxia may result from the diminished circulation. Hypoxia sensitizes cells to hyperthermia damage through a pH-decrease, as is discussed in the chapter on thermobiology. Therefore pressure sites have to be avoided, which can be done by the careful use of cushions.

Circumoral Herpes simplex infection occurred in 10 of the 27 (37%) patients following WBHT. This is within the range reported by others (40 - 50%, Pettigrew et al. 1974A, Barlogie et al. 1979, Moricca et al. 1979). Some authors report that Herpes simplex flares up only after the first WBHT treatment, but our experience is that also after subsequent treatments Herpes simplex may recur (in 4 of 13 cases).

### Severe toxicity

When we started investigating WBHT, we expected to have to deal with some degree of toxicity, but that we would be able to avoid major toxicity by excluding patients who were in a poor general condition. Nevertheless, we encountered severe toxicity, including fatalities. This major toxicity is discussed below, in order of appearance.

#### a) Third degree burns

In two patients third degree burns developed during WBHT which required intensive medical care afterwards. Patient no. 3 was even disabled for several weeks of his short-lasting life, due to the burns of his toes.

In case no. 1, the cause of the third degree burn was obviously the simultaneous induction of local hyperthermia by E.M. radiation. As we have experienced more recently during local hyperthermia treatments, not any amount of thermometry probes placed within the heated tissue can guarantee the absence of unobserved hot spots (Van der Zee, et al. 1986). When the patient is conscious, cooperative and has normal pain sensation in the area treated, (s)he warns so that the local energy input can be reduced by either changing the applicator position or by reducing the overall energy output. Patient no. 1 however was under general anaesthesia during her third treatment and the thermometry probes were apparently not located at the site of the hot spot. There are two probable causes for the development of a hot spot in this patient. Firstly, the area locally heated was the chest wall with ribs underlying the tumour. Microwaves can be reflected by bone and, when they are in phase with incoming waves, form a standing wave. In the area of a standing wave the electrical field amplitude doubles, which results in a quadruplication of the energy level. Secondly, hyperthermia can induce stoppage of circulation when the dose administered is sufficiently high, as discussed in the thermobiology chapter. Either one of these, or both factors together may have resulted in the severe burn. This event made us decide to never again use E.M. heating in an anaesthetized patient unless sufficient temperature monitoring systems are developed. The development of the severe burns in patient no. 3 can be, retrospectively, explained plausibly as follows. The feet of this tall man (length 1.90 m) were lying in the air current immediately coming from the electrical heater below the mattress, of which the temperature may have been over 60°C. Although skin circulation in general increases during WBHT as a consequence of the attempt of the heat regulating system to maintain normothermia, this may have been not the case in the toes. Circulation to the toes may have been reduced due to local blood pressure insufficient to overcome the difference in height. The combination of resulting hypoxia and high local temperature can have caused the burns. As a consequence of this event, all subsequent patient's feet were isolated from the air by a piece of cotton, or later in the series, by plastic foil. Following this procedure, toe burns were not observed anymore.

#### b) Liver damage

Two patients suffered post-treatment clinical jaundice and one of them died with massive liver necrosis (no. 18). Pettigrew et al. (1974A) related liver damage to the height of the applied temperature; they observed no increases in

SGOT levels with treatment temperatures below 41.8°C. Levin and Blair (1978) also reported that they saw no liver problems after they had restricted the treatment temperature to a maximum of 41.5°C. We could not find a correlation between liver damage and hyperthermia dose in our patient series. Larkin et al. (1977) observed SGOT increases in many patients, but they treated patients who already had increased SGOT levels before treatment. One of Levin and Blair's (1978) patients died with massive liver necrosis, but this patient had used phenobarbital for many years and the authors attributed the liver failure to this.

In contrast to the experiences mentioned above, Barlogie et al. (1979), Bull et al. (1979) and Moricca et al. (1979) found no significant changes or only minor elevations in SGOT levels in a total of 48 patients at treatment temperatures of 41.8-42°C.

After the death of patient no. 18, exhaustive analysis of her case history and of all of the treatment parameters was performed. A number of mechanisms which could have lead to liver damage was extensively discussed, as listed below.

- viral hepatitis. Australia antigen, determined as part of the pre WBHT screening, was negative; this however does not exclude viral hepatitis.
- hyperthermia dose. This had certainly not been higher in this patient than in the other patients treated.
- disseminated intravascular coagulation (DIC). Platelet numbers and blood levels of fibrinogen and FDP following WBHT were indicative for DIC, but histological examination had not revealed DIC within the hepatic vessels.
- endotoxins. It is thinkable that the absorption of endotoxins from the intestinal tract is increased under hyperthermic conditions, and that the liver reticuloendothelial system functions at a decreased level, resulting in endotoxin overload of the circulation. The clinical course in this patient however was not typical for that of endotoxin toxicity, which includes shock and kidney failure.
- isoniazid. Hepatotoxicity following administration of isoniazid has been reported but the incidence is low (0.1 %; Ellis 1980) and the prognosis is almost always good (Meyer and Hoignę 1980).
- insufficient oxygen delivery to the liver. The cardiovascular and respiratory parameters measured during WBHT in this patient largely were within the range measured in previously treated patients (Faithfull 1983). From the evidence available it was not considered that hepatic hypoxia had occurred.
- halothane toxicity. Other patients had also received halothane but at

lower maximum (0.25 - 1%) concentrations than this patient (1.5%). The conclusion of the "National Halothane Study" ("Subcommittee" 1966) from a retrospective analysis of 254,896 halothane - anaesthesia cases, was that halothane is a safe anaesthetic, but that in rare cases a hypersensitivity to a metabolite of the drug could develop. Our patient however had never before received this drug, which excludes hypersensitivity as cause.

The question is complicated by other factors. The patient had used Isoniazid from 1 week before WEHT. Isoniazid has been described to enhance, following 7 - 20 days administration, in vitro hepatic defluorination of various fluorinated ether agents (Rice et al. 1980). Furthermore, hepatotoxic metabolites can be produced during halothane metabolism, especially in the hypoxic liver (Keeling and Thompson 1979) Although the parameters measured did not indicate that hepatic hypoxia had occurred, this could not be excluded either.

Benumof et al. (1976) describes two cases in whom the occurrence of a marked selective decrease in hepatic arterial bloodflow was documented by arteriography during halothane anaesthesia. It can not be excluded that a combination of these factors - e.g. hypoxia induced by halothane-induced decreased hepatic bloodflow, hypoxia-induced and isoniazid-enhanced production of hepatotoxic metabolites of halothane, this all further complicated by hyperthermia - may have resulted in massive liver necrosis. But, as listed above, other causes of liver necrosis could not be excluded.

All together, this problem could not be solved. As a result of this event, it was decided to attempt to measure liver bloodflow (HBF) during WEHT with indocyanin green (ICG) extraction.

These attempts to estimate HBF with ICG under WEHT were not successful, the values obtained being improbably large (Wike-Hooley et al. 1983). Once heating had started the estimated values rose to levels that in some cases should be more than 50% of the cardiac output. This is considered improbable in view of the marked peripheral vasodilatation that occurs during WEHT. Lees et al. (1982) have calculated that more than 50% of the cardiac output flows through the skin during WEHT at 41.5°C. The hepatic flow values were derived from ICG extraction of which the values dropped to levels normally found only in patients with cirrhosis or jaundice (Cherrick et al. 1960; Caesar et al. 1961, Reemtsma et al. 1960, Wiegand et al. 1960, Leevy et al. 1962). A decrease in

ICG extraction is indicative either of an increase in flow or of a diminished hepatocyte function. In this case, an increase in flow is unlikely. Moreover, it was observed that the decrease in extraction was greatest in the two patients with pronounced post-treatment SGOT elevations; thus, it would appear that, during the hyperthermic treatment, liver function was changed such that a reduction in the extraction of ICG by the hepatocytes occurred. This change may also account for the liver damage seen following treatment. Recent experiments with pigs (Faithfull 1983) indicate that extraction of ICG is reduced at 39°C and Pettigrew (1975) reported a reduction in BSP metabolism as a result of WBHT. If, however, the liver is extracting less ICG while the infusion rate is unchanged, an increase in the arterial concentration is to be expected, but this was not seen in our patients. ICG is known to bind strongly to plasma albumin and Keys and Taylor (1935) claim that albumin passes rapidly through the capillary walls during severe exercise, thus presenting the possibility of extrahepatic removal routes for ICG during WBHT. Decreases in blood haematocrit which we observed during treatment is likely evidence of haemodilution. A red blood cell volume correction was made in the calculations, but this assumed that the total blood volume remained constant, which may not have been the case. A third possibility is that ICG crosses the intestinal mucosa during WBHT (Nielsen 1963). Most patients suffer from gastrointestinal distress to some extent following treatment (diarrhoea, vomiting), indicating irritation of the bowel.

The question remains however as to what caused the changes in extraction. The effects of heat on the liver have been studied experimentally by several investigators and the results are confusing. If liver metabolism were to increase at higher temperatures as seen by some workers (Cavaliere et al. 1967), this would increase the need for oxygen and therefore for blood. It is likely however that HBF decreases rather than increases during WBHT. Certainly, the induction of anaesthesia reduces HBF, as has been measured by the same technique as used by us (Epstein et al. 1966, Price et al. 1966, Kennedy et al. 1970, Cooperman 1972), and this is aggravated by the use of mechanical ventilation (Cooperman 1972, Lees et al. 1980). Hyperthermia also reduces HBF (Kennedy et al. 1970, Lees et al. 1980), particularly as a result of the shunting of large volumes of blood through the skin (Lees et al. 1982). A combination of an increase in metabolism and a reduction in HBF represents a double risk to the liver. Firstly, extra metabolic heat produced by the liver will not be removed as efficiently, and this could result in selective heating of the liver. Indeed, several workers have measured higher liver temperatures

as compared with "core" temperatures during WBHT in experimental animals (Dickson et al. 1979, Cetas et al. 1980, Fletcher et al. 1982). This suggests the possibility of local heat damage in the liver which would not necessarily correlate with a representative "core" temperature. The one measurement of liver temperature (within a hepatic vein) in our series, which was 0.1 - 0.2°C above oesophageal temperature during the plateau phase, is not necessarily contradictory to this suggestion. Secondly, there is the possibility of hypoxic conditions occurring in the liver. Lees et al. (1982) warn that hepatic hypoxia may occur during WBHT. Although the human liver can withstand a long period of anoxia at normothermia (Nordlinger et al. 1980), this period is likely to be considerably shortened at higher temperatures. Experiments on animal livers (Brauer et al. 1963, Skibba and Collins 1978, Collins and Skibba 1980, Collins et al. 1980) indicate that liver function is diminished at higher temperatures, an effect that could be due to factors other than a direct effect of heat alone. Streffer et al. (1979) have demonstrated a change in metabolism during hyperthermia which results in the production of large quantities of Bèta hydroxybutyrate, a strongly acid product that could disturb normal functioning of enzymes as a result of unfavourable pH. There is also evidence that the hyperthermic liver is rapidly depleted of glycogen (Brauer et al. 1963, Streffer et al. 1979), although energy requirements necessary to maintain metabolic processes are increased (Collins et al. 1980).

The slow plasma disappearance of ICG following WBHT indicates that liver function did not return directly to normal at normothermia. Our data are insufficient to determine how long the effects of treatment on the liver lasted, but Pettigrew determined a mean value of 3.8 days on the basis of BSP excretion tests (Pettigrew 1975). Others have also found reduced clearance of ICG following periods of continuous infusion and there is evidence for saturation of the liver (Reemtsma et al. 1960, Kennedy et al. 1970). Plasma disappearance rates as slow as those seen by us (figure VI-10) however, have been reported only in patients with serious disturbances of liver function (Cherrick et al. 1960). The curvilinear decay is a normal phenomenon and occurs after about 20 min of monoexponential decay in normal individuals (Cherrick et al. 1960, Wiegand et al. 1960, Leevy et al. 1962) but later in abnormal subjects (Wiegand et al. 1960).

In conclusion, the reduced extraction of ICG during and following heat treatment indicates that WBHT disturbs liver function. This makes the use of ICG unsuitable in the measurement of HBF during WBHT, although extraction can still be used as an indicator of liver function. The lack of correlation be-

tween heat dose or T max and liver damage suggests that WBHT results in a combination of physiological and metabolic changes rather than a direct action of heat alone.

#### Respiratory distress syndrome

Patient no. 27 developed an adult respiratory distress syndrome (ARDS) and as a result died 7 days after WBHT. As far as we know, this syndrome following WBHT has been observed earlier only by Greenlaw et al. (1980B). A hypothetical explanation for the development of this complication is that, when one lung is mostly taken up by tumour, the greater part of the pulmonary circulation passes through the other lung. When the cardiac output increases during WBHT, the blood flow in the healthy lung reaches a very high velocity, the endothelial barrier is injured and protein leaks into the alveoli causing the respiratory distress syndrome (Staub 1981). Our patient and Greenlaw et al.'s patient both had one lung completely replaced by tumour. The pretreatment ventilation parameters in patient no. 27, however, were only slightly diminished; we had therefore considered that he should be able to withstand the treatment.

WBHT resulting in death of patients has been described by several other authors. Death was ascribed to cardiac failure (Pettigrew et al. 1974A, Priesching et al. 1976), respiratory failure (Pettigrew et al. 1974A, Priesching 1976, Parks et al. 1979, Herman et al. 1982, Koga et al. 1985), massive liver necrosis (Larkin et al. 1977, Levin and Blair 1978, Herman et al. 1982, Koga et al. 1985), disseminated intravascular coagulation (Pettigrew et al. 1974A), massive tumour necrosis causing an overload of toxic products in the circulation (Pettigrew et al. 1974A, Priesching 1976), brain oedema (Priesching 1976), and to haemorrhage of (regressing) tumours (Priesching 1976, Levin and Blair 1978, Koga et al. 1985). With proper pretreatment examination, some patients who are at high risk for serious complications following WBHT can be excluded from treatment, for instance, those patients who have decreased cardiac and/or respiratory reserve, or patients with tumour involvement of the liver or brain. Unfortunately, our experience has shown that even extensive pre-WBHT screening may not be always sufficient to prevent serious complications or even lethality.

Almost all investigators reporting results of WBHT were confronted with some form of toxicity. It should be mentioned here that recently, there have been

more optimistic reports from a group in Wisconsin, treating conscious patients with WBHT using radiant heat to increase body temperature up to 42°C, almost on an "out patient" basis. In over 170 treatments, no toxicity was observed (Robins, 1986).

#### Induction of metastasis by WBHT?

The data on metastasis induction by hyperthermia (whole body as well as local) are not conclusive. Several investigators have reported on an increase in metastasis rate following hyperthermic treatment of experimental animal tumours as well as on a change in metastasis pattern, whereas others could not demonstrate such differences. A review on this subject was given by Hill and Denekamp (1982). WBHT was subject of 6 studies. Either earlier appearance or increased incidence of metastasis was found in 4 studies. Yerushalmi (1976) who studied local HT as well as WBHT in mice, assumes that a negative temperature gradient between tumour and core may be responsible for increased metastasis. Simultaneous administration of cytotoxic drugs may nullify the increase (Oda et al. 1985).

A highly increased rate of bone metastasis (86%) was found by Lord et al. (1981) following WBHT in combination with radiotherapy in dogs with spontaneous osteogenic sarcomas. In general, bone metastasis was observed in only 5% of dogs with this type of cancer; the common pattern shows lung metastasis. Bone metastasis was found even in one dog with controlled local disease following WBHT, which excludes re-seeding as the origin. These results suggest that WBHT carries the risk of induction of metastasis.

Local hyperthermia appears to be less risky, especially when given in combination with radiotherapy (Hill and Denekamp 1982). The use of thermometry probes within the tumour appears not to increase the risk of metastasis (Walker et al. 1978).

It is not necessary to discuss here that the development of tumour metastasis is a complex process. Factors which may be involved in enhancement of metastasis rate are influenced by hyperthermia such as

- increase in blood flow within the tumour, which may facilitate the release of tumour cells into the circulation;
- loosening of the tumour vessel's endothelium cell lining with the same result;
- weakening of the host's immune defense, leaving more circulating tumour cells alive;



- damage of the recipient organs which may increase the chance of tumour cell lodgement;
- altered blood coagulability: the intravascular coagulation as observed by many WBHT investigators may take place around tumour cells - which may be the first step of metastasis (Hilgard 1980).

In the list above, many uncertainties are included. In the present study, 14 of the 27 patients had already metastasized tumours when they were referred for WBHT treatment and therefore are not evaluable for studying induction of metastasis. Of the 13 remaining patients, 6 developed metastasis in a period 2 - 29 months following their first WBHT. In none of these cases metastasis was considered surprising, regarding the pretreatment status including large inoperable tumours and, in some cases, the long previous history. Neither the time period between WBHT and the clinical evidence of metastasis nor the localization of metastatic lesions was uncommon.

In conclusion: the present study gives no indication that metastasis is induced by WBHT.

#### Survival time

Survival time is a parameter too insensitive for the evaluation of WBHT effect in a clinical study of the type presented here, because a control group could not be included. In the following, 4 patients will be discussed in whom the survival time was, or was suspected to be, negatively influenced by WBHT.

Two patients died as a consequence of WBHT treatment. In one patient (case 18) this meant a considerable decrease in survival time. Although she was found to have occult liver metastasis, she could have lived without symptoms for quite some time. The second patient (case 27) who died was already in such a bad condition before treatment that he was expected to stay bedridden until death when untreated.

Two other patients (nos. 9 and 21) died within one month following WBHT treatment, due to progression of previously known tumour deposits.

In case 9 it was suggested that WBHT had caused an increased progression of the carcinomatous lymphangitis of the lungs. This was based on the worsening of her respiratory condition and on the increase in abnormalities on the X-ray of the chest, following WBHT. As both the respiratory function and the X-ray picture had improved again one week later, we assume that the temporary worsening most likely resulted from fluid accumulation around the tumour

deposits in the lungs. In case 21, the findings during autopsy were considered unusual: metastatic nodules of malignant mesothelioma were found in both pleural cavities, within the lungs, the pericardium and the abdominal cavity. The primary tumour had grown continuously through the diaphragm into the abdominal cavity resulting in a large retroperitoneal tumour. It was suggested that this overwhelming tumour metastasis could have been caused by the hyperthermic treatment. Considering the short time available and assuming that the minimum tumour volume doubling time observed in humans is 312 hours and that tumour deposits become clinically identifiable when  $10^8$  cells are present (Hermens 1984), this cause-and-effect relationship is unlikely.

The one-, two- and three-year survival rates observed in our patient material are 26, 15 and 7%, respectively. These data are not comparable with any other list of survival rates; the history of each patient has to be judged individually. As all patients were characterized by an inferior prognosis, the quality of life during the period of survival is of more relevant importance.

#### Profit score

A judgement of profit score cannot be discussed for the group of patients as a whole; there is no similar group of patients available for comparison. For each individual patient the balance between beneficial effect and undesirable side effects has been drawn up separately. Even for the individual patient - and treatment - the weighing procedure is extremely difficult. In fact, the judgement of profit score represents the clinician's subjective view on the question if the treatment would have been given if the outcome would have been known before. Even with a remarkable objective tumour response, the final result can be judged negative.

As an example patient no 9 can be mentioned. One should judge how positive the achievement of complete regression following WBHT and 18 Gy is when the patient dies 3 weeks later of an unexpected progression of carcinomatous lymphangitis in the lungs. We decided the profit to be negative.

Another example given is patient no 8, who was very enthusiastic about the treatment when she left hospital completely free of pain, but considered this effect not worthwhile anymore when the pain had returned three weeks later. The profit for this patient is therefore also scored negative.

The stress of WBHT was also judged differently by each individual patient. Some patients felt tired for weeks following WBHT, whereas others had completely recovered 1 day following WBHT. One patient even asked for his second

"sauna treatment". Therefore we decided the treatment was worthwhile when there were no or only minor complications of the WBHT-treatment, and when there was at least a "no change" or a considerable palliation for a duration of 2 months.

The final conclusion is that the outcome for the patient was beneficial following more than half of the treatment regimens (19/30). On the other hand, the outcome was clearly negative following 11 treatment regimens.

#### Profit from WBHT

The judgement on profit score described above does not include a judgement on the additional effect of WBHT treatment on the clinical outcome. An estimation of this additional effect can be made by, again, looking at each individual patient. For most patients, the question whether WBHT has added substantially to the result obtained, remains unanswered. As an example, patient no. 13 (adenocystous carcinoma initiating from the parapharyngeal space) can be mentioned. In this patient the primary tumour was already in regression following the first series of radiotherapy combined with misonidazole. The contribution of WBHT to the positive clinical outcome -this patient is the only really long-term surviving patient- cannot be assessed. Another example is patient no. 20 (inoperable adenocarcinoma of the sigmoid). The clinical outcome achieved -"no change" for a duration of 7 months- could also have been achieved by the high dose of radiotherapy only.

For some other patients, the clinical outcome was remarkable, which was not expectable following treatment with the conventional modality (i.e. radiotherapy or chemotherapy) only. In patient nos 5 and 6 for example (lung adenocarcinoma), it was not expected a priori to achieve local tumour control by radiotherapy alone and, furthermore, in patient no. 5 a complete regression had been achieved following WBHT and 24 Gy only. The additional effect of WBHT in patient no. 5 was established later in his history by comparing the effect of radiotherapy alone (50 Gy) and radiotherapy (46.5 Gy) + WBHT on two groups of previously non irradiated lymphnodes (table VI-9). The clinical outcome following the combined treatment was better than that following radiotherapy alone. Remarkable results which we dare to ascribe to the additional effect of WBHT were also observed in patients no. 10 and 11. In patient no. 10 (locally recurrent colon adeno carcinoma), partial response and considerable palliation were achieved following WBHT and a radiotherapy dose as low as 19.5 Gy. Patient no. 11 (mesothelioma) was disease free for a duration of 21 months following WBHT and 19.5 Gy radiotherapy, whereas mesothelioma is known to be a

relatively radioresistant tumour (Brady 1981). In two other patients (no. 12: lung metastasis of osteosarcoma; no. 14: fibrosarcoma in the sacroiliacal joint), the additional effect of WBHT is also indicated by the clinical outcome. In patient no. 12, 49 Gy had been given up to 1 week before the combined treatment, without any effect on tumour sizes, whereas the combined therapy resulted in some (less than partial) regression within two weeks. In patient no 14 (fibrosarcoma in the sacroiliacal joint) partial regression was observed following only 20 Gy and WBHT, plus immediate palliation following WBHT. As this patient series was not included in a comparative, prospective randomized, study, the additional effect of WBHT cannot be proved. The results however indicate that (whole body) hyperthermia, if it can be administered with only minor toxicity, can provide a valuable treatment modality in addition to radiotherapy, for radioresistant tumours.

#### Are there future indications for WBHT?

The final conclusion from this study is that WBHT at 41.8 - 42°C, in combination with radiotherapy, can be an effective therapy regimen for cancer. Nevertheless, the WBHT treatment procedure described in this report does not seem to be generally indicated since the possibility of the occurrence of fatal complications is not predictable, even with extensive pretreatment examinations. This unpredictability of severe toxicity implies that the application of WBHT with the described method is not indicated in patients without severe complaints and with a relatively good prognosis. In patients with a poor short term prognosis, with disabling pain and with the possibility of additional treatment with a low dose of radiotherapy, the small risk of fatal complications has to be weighed by the patient against the good chance of a palliative effect. It is questionable if this is a realistic indication in present society, where economizing measures in public health service are an every day issue. Calculations on the cost of WBHT were performed by Greenlaw et al. (1980A). There were some differences in the application of WBHT by Greenlaw's group and ours: Greenlaw et al. used the technique of immersion of the patient in molten paraffin and their monitoring schedule was somewhat less extensive than ours. The total cost of 1 WBHT session was calculated to be US\$ 3.191. The costs of general anaesthesia and intensive monitoring of physiologic parameters amounted to about 70% of the total cost. Fortunately the possibilities for treatment of pain have considerably improved, so that almost all patients suffering pain from malignant tumours can be successfully treated

by methods which are less expensive and intensive than WBHT.

Therefore it has to be concluded that WBHT using the procedure as described in this report has no future indications. This does not imply that WBHT should be abandoned altogether, but rather that different methods of administration should be explored. If it can be demonstrated that WBHT can be applied simply and safely, for instance by applying WBHT at moderate levels ( $< 41^{\circ}\text{C}$ ) or by using the "radiant heat method" (Robins 1986), WBHT may, indeed, play a greater role in future cancer therapy. There are at least two categories of patients which may benefit from this approach.

I Patients with localized radio-resistant tumours. These patients may be treated with WBHT at  $40^{\circ}\text{C}$ -  $41^{\circ}\text{C}$  to support deep local tumour heating, in addition to radiotherapy, since one of the problems with deep local heating will be the cooling effect of the blood entering the tumour at core temperature. Experimental and clinical studies have demonstrated a correlation between the hyperthermia dose at the coldest spot in the tumour and the therapeutic result: the chance of complete response and local control increases when this "minimum hyperthermia dose" increases (Dewhirst et al. 1984, Oleson et al. 1984, Van der Zee et al. 1986). Preheating of the blood by means of WBHT guarantees a given minimum hyperthermia dose.

In these patients, addition of hyperthermia to radiotherapy may improve both local control and cure.

II Patients with metastatized tumours. These patients may be subjected to WBHT at  $40 - 42^{\circ}\text{C}$ , in combination with, or in addition to, chemotherapy. As described before (chapter II), it is not yet clear whether simultaneous administration of WBHT and chemotherapy will result in therapeutic gain. However, the least therapeutic gain which can be expected from a combination of both modalities is an additional effect of hyperthermia on the tumour, without extra normal tissue toxicity, when the treatments are given sequentially.

### Conclusions

The technique used for induction of WBHT is clinically useful: its efficiency is comparable to the efficiencies mentioned by other authors who use a technique of transcutaneous energy input and the temperature distribution achieved is satisfactorily homogeneous. The hyperthermia dose achieved with WBHT (2 hrs. at  $41.8^{\circ}\text{C}$ ) does not influence tumour pH, so that no additional therapeutic effect through a heat induced acute pH decrease can be expected.

The WBHT-dose kills only part of the tumour cell population so that WBHT has to be combined with another treatment modality to achieve an effect which is valuable for the patient. In our series, the clinical outcome was beneficial in 63% of the cases. In some cases however, lethal toxicity was induced by the WBHT treatment unexpectedly. This unexpected toxicity, together with the complexity, and therefore the high cost of the method used, implies that the application of "adapted Pomp-Siemens cabin method"-induced WBHT will hardly ever be indicated.

The positive therapeutic results, however, encourage continuation of research into better alternatives such as local hyperthermia and/or safer methods of WBHT-induction.

SUMMARY

SAMENVATTING

GLOSSARY OF ABBREVIATIONS

REFERENCES

DANKWOORD

CURRICULUM VITAE





## SUMMARY

Whole body hyperthermia is one of the methods available for the treatment of malignant tumours with heat. At the Rotterdam Radio-Therapeutic Institute this method was investigated in 27 patients in a period of 3½ years.

This thesis describes the results of this investigation.

In Section I a review is given of the background of hyperthermia in cancer treatment. The history of hyperthermia and the objectives of the study are discussed in Chapter I. Publications on this subject can be traced to ancient times, although upto the start of this century these deal mainly with cauterization and fever therapy.

In Chapter II the results of experimental research are discussed. Experimental research has resulted in important starting points for clinical research: hyperthermia specifically damages tumour tissues but when hyperthermia is given alone, it will hardly ever be possible to obtain complete tumour regression. The combination with radiotherapy appears optimal: the two treatment modalities have additive, complementary effects and hyperthermia enhances the effect of radiotherapy, which may result in therapeutic gain. This makes clinical investigation worthwhile.

In Chapter III normal thermoregulatory mechanisms and temperature distribution within the body under various circumstances are discussed, resulting in guidelines for temperature measurement during WBHT. The various techniques available for the induction of hyperthermia in patients are described.

The investigations performed prior to the start of the clinical WBHT treatments are presented in Section II (Chapter IV). These encompass animal experimental work done in our own department, as well as a search through literature in order to gain insight in potential toxicity. Some WBHT treatments in another clinic were attended and active participation in some fever therapies took place.

This "preclinical" research resulted in guidelines for patient selection before and monitoring procedures during and following treatment with WBHT.

In Section III the present treatment series in 27 patients is described. The treatment procedure, including pretreatment examinations, monitoring during and following WBHT and summaries of the case history of each patient are presented in Chapter V. This is followed by the results in Chapter VI, which deals with the heating technique, tumour response and palliation, and toxicity.

These results are discussed and compared to those of other investigators in Chapter VII, followed by evaluation of the potential value of WBHT.

The final conclusions from this study are:

- the technique used for induction of WBHT is clinically useful and its efficiency is comparable to the efficiencies mentioned by other authors who use a technique of transcutaneous energy input;
- WBHT at 41.8°C for 2 hours is effective, but has to be combined with either radiotherapy or chemotherapy to obtain a valuable effect for the patient;
- In some cases the treatment may unexpectedly induce severe toxicity. Therefore research should continue with regard to better alternatives such as local hyperthermia and/or a safer method of WBHT-induction.

# SAMENVATTING

Totale lichaamshyperthermie is één van de mogelijke technieken om kwaadaardige tumoren met warmte (hyperthermie) te behandelen. In het Rotterdamsch Radio-Therapeutisch Instituut werd deze methode onderzocht bij 27 patiënten, in een periode van 3½ jaar.

In dit proefschrift worden de resultaten van dit onderzoek beschreven.

In deel I wordt een overzicht gegeven van de achtergronden van warmtebehandeling. In hoofdstuk I wordt een kort overzicht gegeven van de geschiedenis van behandeling met hyperthermie, en van het doel van deze studie. De geschiedenis begint al heel lang geleden, al werd vóór het jaar 1900 vooral gepubliceerd over resultaten verkregen met cauterisatie en koortsbehandeling.

In hoofdstuk II wordt ingegaan op de resultaten van laboratoriumonderzoek. Laboratoriumonderzoek heeft een aantal belangrijke uitgangspunten opgeleverd: hyperthermie beschadigt specifiek kankerweefsel, maar met hyperthermie alleen zal het vrijwel nooit mogelijk zijn om tumoren helemaal te laten verdwijnen. De combinatie met bestraling lijkt de beste toepassing te zijn: beide behandelingen vullen elkaar aan en bovendien wordt het effect van bestraling versterkt door hyperthermie, wat kan resulteren in therapeutische winst. Deze bevindingen maken klinisch onderzoek de moeite waard.

In hoofdstuk III wordt beschreven hoe onder normale omstandigheden de lichaamstemperatuur onder contrôle gehouden wordt en op welke plaatsen temperaturen gemeten moeten worden om de lichaamstemperatuur veilig te kunnen verhogen. Verder wordt aangegeven met welke technieken tumoren, of patiënten verwarmd kunnen worden.

In deel II (hoofdstuk IV) wordt ingegaan op het onderzoek dat werd verricht alvorens in het RRTI met de behandeling van patiënten begonnen werd. Dit was deels eigen onderzoek, o.a. het uitvoeren van experimenten met proefdieren om de techniek te leren beheersen en een eerste indruk van de bijwerkingen te krijgen, en deels literatuuronderzoek naar de bijwerkingen van hyperthermie en de behandelingsresultaten van anderen met totale lichaamshyperthermie. Ook werden hyperthermie-behandelingen in een ander centrum bijgewoond en werd ervaring opgedaan met koortsbehandeling bij enkele patiënten. Zo konden beleidslijnen opgesteld worden m.b.t. de patiënten die binnen het RRTI behandeld zouden gaan worden. In dit deel wordt ook de apparatuur beschreven die beschikbaar was voor het verwarmen van patiënten.

In deel III wordt ingegaan op de behandeling van de 27 patiënten binnen het RRTI. In hoofdstuk V worden de gevolgde procedure, het onderzoek voor, tijdens en na de behandeling en de ziektegeschiedenissen van elke patiënt afzonderlijk, beschreven. In hoofdstuk VI volgen de resultaten: de effectiviteit van de behandelingsmethode (met name de snelheid van opwarmen), de gunstige effecten (het slinken van tumoren en/of het verdwijnen of verminderen van pijnklachten), en de - ongewenste - nadelige bijwerkingen. In hoofdstuk VII tenslotte worden deze resultaten vergeleken met die van andere onderzoekers en wordt de waarde van de behandeling besproken.

De conclusies luiden als volgt:

- de techniek van verwarmen is bruikbaar en even efficiënt als andere technieken waarbij warmte toegevoerd wordt via de huid van de patiënt;
- totale lichaamshyperthermie, waarbij een dosis van 2 uur  $41.8^{\circ}\text{C}$  toegediend wordt, is effectief, maar voor het bereiken van een zinvol effect voor de patiënt moet de behandeling gecombineerd worden met bestraling of chemotherapie;
- de behandeling resulteerde soms in onverwacht ernstige bijwerkingen; daarom moet voor toekomstige toepassingen van hyperthermie gezocht worden naar betere alternatieven, zoals plaatselijke toediening van hyperthermie en/of een veiliger methode voor totale lichaamshyperthermie.

## GLOSSARY OF ABBREVIATIONS

ARDS	adult respiratory distress syndrome
BCG	Bacille Calmette Guérin
BCNU	bis-chloroethylnitrosurea
BSP	bromsulphalein
C	chemotherapy
ca	carcinoma
Ca <sup>++</sup>	ionized calcium
CCNU	cyclohexylchloroethylnitrosurea
cGy	0.01 Gray (unit of absorbed radiotherapy dose, in J/kg)
cis Pt	Cisplatinum = cis-diamminedichloroplatinum (II)
Cl <sup>-</sup>	ionized chloride
C parvum	Corynebacterium parvum
CR	complete response
CT	computer tomography
DIC	disseminated intravascular coagulation
DTIC	dimethyl-trianzeno-imidazole-carboxamide
ECG	electrocardiogram
EHBF	estimated hepatic bloodflow
E.M.	electromagnetic
FDP	fibrinogen degradation products
5 FU	5-Fluorouracil
Gy	Gray (unit of absorbed radiotherapy dose, in J/kg)
H/HT	hyperthermia
HBF	hepatic blood flow
HIDA	N(2,6-diethylacetanilido)imino-diacetic acid
ICG	indocyanine green
INH	isoniazid
J	joule
K <sup>+</sup>	ionized potassium
LCOF	liquid crystal optical fiber
LDH	lactic dehydrogenase
LHT	local hyperthermia
MeCCNU	methyl CCNU
MHz	MegaHerz
n	number of data/patients
Na <sup>+</sup>	ionized sodium

NC	no change
$P^-$	ionized phosphate
PR	partial response
Pt	patient
r	correlation coefficient
R/RT	radiotherapy
RHT	regional hyperthermia
S	surgery
s.d.	standard deviation
S.E.M.	standard error of the mean
SGOT	serum glutamic oxalacetic transaminase
SGPT	serum glutamic pyruvic transaminase
S phase	synthesis phase (in cell cycle)
t	time
T/temp	temperature
$^{99}\text{Tc}$	$^{99}$ Technetium
TER	thermal enhancement ratio
$T_{\text{rect}}$	rectal temperature
$T_{\text{tum}}$	tumour temperature
$T(\ )_{\text{max}}$	highest temperature recorded at site
WBHT	whole body hyperthermia
WHO	World Health Organization

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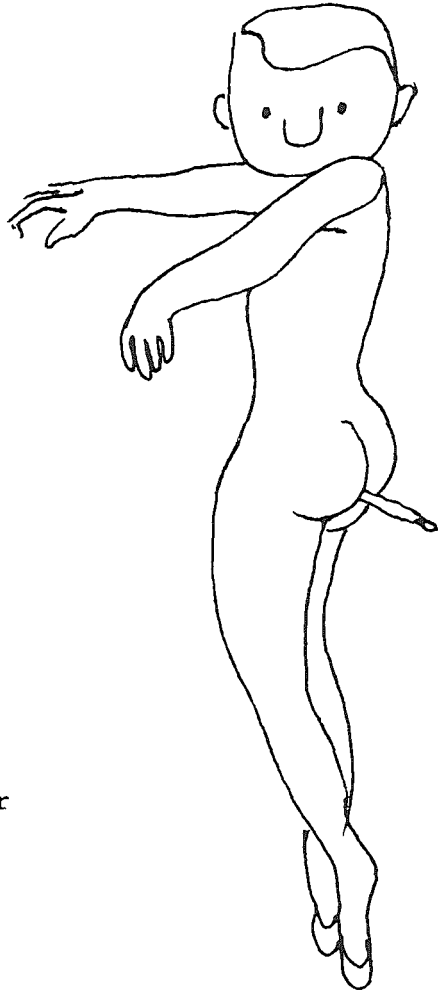
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koorddanser = rope walker

koord (kə:d) = rope

koorts (kə:dʒ) = fever

*Koorts danser*

Uit "Clownerietjes" van Toon Hermans, een uitgave van Elsevier.

## CURRICULUM VITAE

De schrijfster van dit proefschrift werd op 4 juli 1954 te Zwartewaal geboren. In 1971 behaalde zij het diploma HBS-B aan de Chr. Scholengemeenschap "Blaise Pascal" te Spijkenisse en begon de studie Geneeskunde aan de Universiteit van Amsterdam.

Na het kandidaatsexamen in 1974 werd de studie voortgezet aan de Rijksuniversiteit te Leiden, alwaar in 1978 het artsexamen afgelegd werd. Sindsdien werkt zij, binnen het Rotterdamsch Radio-Therapeutisch Instituut, aan klinisch onderzoek naar de toepassingsmogelijkheden van hyperthermie bij de behandeling van kanker. De eerste jaren als medewerkster van de afdeling Experimentele Radiotherapie van de Erasmus Universiteit Rotterdam, vanaf 1983 in dienst bij het Rotterdamsch Radio-Therapeutisch Instituut, echter steeds in de groep van prof. dr. H.S. Reinhold.

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