Warmth Organization and Disease

"I would cure all diseases if I only could produce fever."

Parmenides (Greek philosopher, 510 BC.)

2.1. Introduction

During the evolution of vertebrae, from fish to amphibians, from birds to mammals, the development of a warmth organism, or warmth organization can be observed, through which the organism becomes gradually independent from temperatures of the surroundings. In humans, the regulation of body temperature is most developed. Especially in humans, the blood flow through the skin is more developed than in any other mammalian organism, and serves the regulation of body temperature through vasoconstriction and vasodilatation, and through production and perfusion of sweat by the sweat glands. Missing a thick layer of hair (fur), the human body is very open to changes of temperature in the environment. Therefore, in order to maintain a stable core temperature, the human organism must be able to adjust to changes in temperature quickly, easily and effectively.

Isothermia and augmentation of adaptation to changes in temperature are evolutionarily connected with the development of the circadian rhythm of the core temperature. In addition, the exchange of warmth between core temperature and the temperature of the environment, or periphery, or skin is another example for the augmentation of the possibilities to maintain a stable core temperature.

Newborns have not yet developed a functioning circadian rhythm. Only after about 4 weeks, day rhythms start to occur. In adults, the circadian rhythm forms a sinus curve with maxima and minima around 6.00 oclock a.m. and p.m. The amplitude is usually around 0.6°C.

In cancer patients, and patients with other chronic diseases, like chronic viral infections and degenerative diseases, not only the circadian rhythm of the core temperature changes significantly and becomes chaotic, but also the amplitude becomes flat and the delicate interaction between core and peripheral temperatures is disturbed. Therefore, in the Cologne Model, patients will undergo therapeutic interventions to improve both their circadian rhythm and its amplitude, and the maintenance of a stable core temperature.

2.2. Total Body Hyperthermia

In the last two decades of the 20th century, a better understanding of the effects of fever has lead to a renewed interest in the immunological effects in acute and chronic diseases. Various organs need a specific temperature to function optimally. The average resting temperature gradient between core temperature and the periphery (skin) is usually from 37 C to 34°C to 25°C at room temperature. The inner organs do not have equal temperatures either. Depending on their metabolic activities and blood perfusion, each inner organ has a different and changing core temperature by itself (kidneys, liver, lungs, testicles, etc.). The only exception might be the mid-brain with its hypothalamus, where functions like breathing, hunger and thirst, sexuality, blood pressure and body temperature are regulated. Here, the core temperature is kept very constant at approximately 37°C.

Of all regulatory systems, the warmth regulation is one of the most developed ones, expressing its importance for the overall survival of the individual.

Transpiration is the visible and invisible mechanism of giving off warmth through the skin to the environment. Sweating is the intensified and noticeable form of transpiration.

However, transpiration and sweating only leads to cooling if the water can be evaporated. Evaporation is one of the most effective ways to get rid of excessive warmth. Evaporation is stimulated by airflow. If there is no airflow, a thin layer of water (sweat) will cover the skin and evaporation becomes almost impossible. In case of total body hyperthermia (TBH), airflow is carefully inhibited, sweating is increased and thus, the loss of warmth is put to a hold and the body temperature rises, producing fever.

Peripheral vasodilatation and increased blood flow will bring more blood to the surface (skin), and the warmer the skin, the better the loss of warmth through radiation of infrared waves (5,000 to 20,000 nm). High-gloss aluminium folia will reflect these infrared waves and bring about an increase of the body temperature in TBH.

There are several methods to increase the core body temperature, ranging from hot water and paraffin baths, sauna and sauna-alike settings, extra-corporal warming of the blood, high-frequency waves and infrared radiation.

In the electro-magnetic spectrum, infrared waves are the first invisible waves next to visible light. The radiation of infrared waves is a characteristic of all bodies above the absolute zero point.

In nature, the sun is the most effective source of infrared radiation, supporting all life processes on earth.

Most of all, short-wave infrared radiation penetrates through the skin and reaches the blood flow under the skin. Through this mechanism, the local blood temperature is increased, spreading the warmth throughout the body and causing the core temperature to rise.

Therefore, in the Cologne Model, total body hyperthermia is brought about through application of short-wave infrared radiation. There are two main components:

1. The actual exposure to the infrared radiation;

2. Simultaneous isolation of the body, causing the core temperature to increase;
3. Reflection of body heat by aluminium folia, adding to the increase of the core temperature.

During the therapy session, the temperature is monitored using a rectal thermometer in situ. In addition, blood pressure and heart function are monitored continuously using an electrocardiogram and a capillary pulse monitor. During the session, there is also intravenous access for application of fluids and medication if necessary.

Usually, in the Cologne Model, patients will undergo a core temperature increase up to 39.5°C to 40°C for the duration of one hour. This is well tolerated.

During the cooling-down phase, the exposure of the body to room temperature starts with the feet and slowly on, the rest of the body, going from cauda to cranium.

2.3. General Phenomena Linked to Hyperthermia

General phenomena linked to hyperthermia are the following:

1. Metabolism and biochemical processes are increased by about 15% per one degree C core temperature increase. This leads to an increased regeneration and repair mechanisms in tissue. One concern is that in increased body temperature, the metabolism and clearance of medication can be increased as well.
2. Sol and gel solutions, as well as lipoids, have the tendency to go into a liquid phase, causing a decrease of the viscosity of extra-cellular body fluids and an increase of cell-membrane elasticity.
3. Passive diffusion through cell membranes is increased.
4. Through increased nerve activity, increased muscle contractibility appears.
5. In small body temperature increases, all phases of cell mitosis are activated. When the core temperature reaches about 40°C, these phases are completely stopped. In abnormal cells (cells chronically infected with a virus, or malignant cells), the inhibition of mitosis is blocked at a much lower core temperature.
6. Increased ergotropic activity of the vegetative nerve system; mainly the sympatic part.
7. Increased sense perception and need to move; occasionally fear and claustrophobia.
8. Activation of hypothalamic-pituitary functions, leading to an increased release of pituitary hormones, affecting the suprarenal glands in particularly.
9. Increased ventilation.
10. Leucocytosis, lymphopenia (caused by activation of the lymphocytes and their subsequent homing), decrease of eosinophils, increase of serum potassium.

2.4. Hyperthermia and the Endocrine System

Hyperthermia does not only cause increased blood perfusion of tissue but also increased release of hormones:

Axis pituitary gland – suprarenal glands

Hyperthermia with a core temperature above 38.5°C. always causes an increased production and release of ACTH with a consequent increase of serum cortisol levels. When the core temperature is elevated, the need for cortisol is increased as well. It is still unclear whether this cortisol release is in access to the needs of the organism.

Thyroid gland

Hyperthermia causes increased release of TSH and subsequent production of thyroid hormone, causing a transient hyperthyroidism. In patients with hyperthyroidism, an increase of the body temperature until 38.5°C. is not contra-indicated.

Pancreas

During hyperthermia, the release of insulin and glucagon are not noticeably increased.

2.5. Hyperthermia and the Immune System

Since there are intimate interactions between the endocrine system, the nerve-sense system and the immune system (as is well-documented in the area of the psycho-neuro-immunology), the effects of hyperthermia on the immune system are many. First of all, the metabolism of immune competent cells (T-lymphocytes) is increased, causing increased compartment shifting, homing and cytotoxicity.

B-cells are activated, which brings about an increase of the production of immunoglobulins.

Phagocytosis is an evolutionary ancient and primitive defence mechanism against foreign bodies and bacteria through incorporation and then intra-cellular digestion of the material. Hyperthermia increases significantly the phagocytic activities of neutrophilic leucocytes and macrophages: increase of temperature correlates positively with the increased phagocytosis.

Already in the beginning of the twentieth century, it was observed that hyperthermia increased the mobility of granulocytes. Recently, it has been well documented that hyperthermia activates compartmental shifting and homing of lymphocytes as well.

Also, the TH1/TH2 response of CD4+ lymphocytes is definitely improved.

2.6. Hyperthermia in Oncology

Rudolf Steiner (1861-1925), founder of the anthroposophical medical movement, already recommended hyperthermia in the treatment of cancer patients. Cancerous cells have a very abnormal and inefficient metabolism. By increasing the core body temperature by two to three degrees, the metabolism of the cancerous cell is put under so much stress, that the cell usually dies. Because of the beneficial effects of hyperthermia on the immune system (see 2.5.) and the initiation of death of cancerous cells, today, hyperthermia plays a significant role in the evidence-based treatment of cancer patients.

In the 1870s, the American surgeon at the Memorial Slaon-Kettering Cancer Center in New York, Dr. William Coley observed that several of his cancer patients with inoperable tumors spontaneously recovered completely after a bout of high fever. These fevers were usually caused by wound infections. This observation led to his interest to treat cancer patients with artificially provoked fever.

Dr. Coley teaching young doctors surgical interventions in the oncological practice.

In the previous decade, in the oncological practice, moderate total-body hyperthermia has experienced a renaissance. There are clinical studies on total-body hyperthermia, in oncological patients as well as in patients with various other diseases, which describe very positive effects on the heart and circulatory system, as well as in bronchial asthma and in immunodeficiencies. Interestingly, most current clinical studies in this area focus on the effects on quality of life, and the smoothening of side effects of chemotherapy and radiation. Also, combination of total-body hyperthermia with chemotherapy and radiation seems to enhance cytotoxicity with fewer side effects.

Furthermore, there is a clear rationale to use total-body hyperthermia in the oncological practice because of its immunomodulating effects. Growth-inhibiting and even complete response in total-body hyperthermia has been demonstrated in animal studies and in patients.

Epidemiological studies have shown a connection between lack of fever and occurrence of cancer as well as spontaneous remission of cancer after a bout of fever (1,2).

Moderate total-body hyperthermia alone causes significant destruction of malignancies (3). Most impressive results have been documented in the treatment of sarcomas, melanomas, and tumors of the gastrointestinal tract (3, 4, 5, 6).

Recent studies showed a clear benefit if local or regional hyperthermia was combined with radiation and chemotherapy, compared to radiation and chemotherapy alone (6). An intratumoral- or core body temperature of 40.0 C was usually reached in all patients.

A very promising new application seems to be the combination of total-body (or regional) hyperthermia and chemotherapy with cytokines (TNF-alpha) (7).

In the Cologne Model, patients will undergo total body hyperthermia. Over a period of about three hours, the core body temperature will be increased to about 40°C and maintained at that temperature level for about one hour. Then, the patient is cooled down again in a one-to-two-hour period. Core body temperature, heart function, blood pressure, and other parameters are monitored continuously during the whole procedure.

2.7. Hyperthermia and heat schock proteins

Hildebrandt et al. evaluated in a phase I/II study the feasibility, toxicity and response rates of von Ardenne's systemic cancer multistep therapy (sCMT) when applied as an adjunct to cytostatic therapy in patients with metastatic colorectal cancer. They found that sCMT was feasible, but associated with a specific spectrum of grade III/IV toxicity (skin 20%, pain 16%, peripheral nerves 8% of treatment courses). The fact that three patients who did not respond to initial chemotherapy achieved a partial response after additional sCMT suggests that sCMT enhances the effect of chemotherapy in patients with colorectal cancer.(8)

Armour EP, et al; found the positive aspects of LDMH-brachytherapy for clinical application are sixfold; (1) the thermal goals (temperature, time and volume) are achievable with currently available technology, (2) the hyperthermia by itself has no detectable toxic effects, (3) thermotolerance appears to play a minor if any role in radiation sensitization, (4) TER of around 2 can be expected, (5) hypoxic fraction may be decreased due to blood flow modification and (6) simultaneous chemotherapy may also be sensitized. Combined LDMH and brachytherapy is a cancer therapy that has established biological rationale and sufficient technical and clinical advancements to be appropriately applied. This modality is ripe for clinical testing.(9)

Superficial bladder cancer can be treated by transurethral resection (TUR) and adjuvant intravesical therapy. Intravesical bacillus Calmette-Guerin (BCG) has been proven to be more efficacious with respect to recurrence prevention than intravesical chemotherapy, although at the cost of more severe side effects. Van Der Heijden AG, et al; Found that the microwave induced hyperthermia combined with MMC has promising value in intermediate or high risk superficial bladder cancer patients compared to literature data of BCG and/or intravesical chemotherapy, particularly where other treatments, i.e. BCG, have failed.(10)

Hyperthermia between 40 and 45 degrees C is now recognized to radiosensitive tumors locally increasing local control. The more recent technological progress show the possibility of heating at depth while controlling temperature. In Germany and Netherland, Marchal C, et al; found that, hyperthermia is a standard treatment for cervix carcinomas and for some sarcomas. Today, only microwave superficial hyperthermia, thermo ablation using either radiofrequencies or high focussed ultrasound, and loco regional heating by intraperitoneal perfusion or by external circulation for tumors of the extremities, are in clinical evaluation in France. Is appears suitable to define clinical French teams, that could evaluate the clinical use of deep heating by the more recent developed techniques.(11)

The 'masking effect' is the observation that heat shock reduces or masks the apparent expression of ionizing radiation (IR) damage to DNA. The mechanism of this effect is thought to involve the aggregation of proteins to the nuclear matrix or chromatin, thereby stabilizing these structures and masking actual DNA damage from assays and presumably from DNA repair complexes. Here it is reported of Wanderwaal RP, et al; that it show the treatment of living cells with reducing agents diminishes the interaction between DNA and Protein Disulphide Isomerase (PDI) and that hyperthermia restored the PDI-DNA interaction, indicating that the masking effect occurred in vivo. Several proteins, including B23 and Hsp60, have been identified whose interaction with DNA increased following heat shock. (12)

Raaphorst GP, et al; tested in a pair of mouse cell (MB+ wild-type and MB-, DNA polymerase beta knockout cells) the thermal radiosensitization and in human breast carcinoma cells (MCF7 wild-type and C716 transfected to give elevated DNA polymerase beta expression). Results showed that neither reducing DNA polymerase beta (involved in base excision repair) nor increasing it had any significant effect on thermal radiosensitization. The data indicated that polymerase beta was not involved in thermal radiosensitization, and since hyperthermia is known as a radiation damage repair inhibitor, other repair pathways might be involved and need to be explored.(13)

Kampinga HH, et al; found that all biochemical and cytogenetic data on radiosensitization by heat treatment at and above 43 degrees C indicate that inhibition of DNA repair plays a central role. There are several DNA repair pathways involved in restoration of damage after ionising irradiation and the kinetics of all of them are affected by heat shock. The data show that thermal inhibition of the non-homologous end-joining pathway (NHEJ) plays no role in heat radiosensitization. Furthermore, limited data suggest that the homologous recombination pathway may also not be a major heat target. By deduction, it is suggested that inhibition of base damage repair (BER) could be the crucial step in radiosensitization by heat. While a lack of mutant cell lines and redundancy of the BER pathway have hampered efforts toward a conclusive study, biochemical and correlative evidence support this hypothesis.(14)

Hyperthermia at temperatures above 41 degrees C denatures a set of thermolabile cellular proteins located in all parts of the cell. Lepock JR et al; found three general consequences of nuclear protein denaturation and aggregation of relevance to cellular damage are: (1) protein (enzyme) inactivation, both direct inactivation of thermolabile proteins and indirect inactivation due to co-aggregation; (2) reduced accessibility and altered physical properties of DNA due to masking by aggregated protein; and (3) protein redistribution into and out of the nucleus. Functional impairment of the nucleus appears to be due to one or a combination of these basic mechanisms.(15)

Selective hyperthermia can be a feasible treatment modality for deep tissue abnormalities. This process has two potential benefits to medical professionals: simplicity of procedure and safety to patient. Cowan TM, et al; propose an optimization coefficient relating the dynamic and geometric parameters of selective hyperthermia, and proceed to measure it in an experimental setup consisting of a near-infrared laser and laser-absorbing dye. Temperature measurements taken at different locations are analyzed so optimization coefficients can be calculated for different parameters. This optimization coefficient compares the difference in temperatures from inside and outside the target. Analysis of the values after thermal equilibrium provides information about the best parameter selection. Based on our analysis, optimization can be obtained by using this coefficient to compare the selectivity of several parameter combinations. (16)

The term "hyperthermia" summarises different procedures of raising the temperature of a tumour-loaded tissue to a temperature of 40-43 degrees C. In this context, locoregional procedures (radiative/capacitive local, interstitial and regional hyperthermia; endoluminal hyperthermia), hyperthermic perfusion techniques (hyperthermic peritoneal and isolated limb perfusion), and whole-body hyperthermia differ with regard to their indication, expenditure of application, and evidence of efficacy. Hildebrandt et al; found that particular progress has been made in regional radiofrequency hyperthermia, where novel multiantenna-applicators and their integration into MR-applicators ("hybrid-systems") have recently been introduced into clinical practice. In addition, combinations of hyperthermia with novel technologies (magnetic fluid hyperthermia, thermosensitive liposomes, immunotherapy, gene targeting) are imminent.(17)

Besides the direct cytotoxic power of hyperthermia there is an immunomodulatory effect and a radiation and chemotherapy sensitizing effect in the heated tissue. Clinical hyperthermia is an invasive or non-invasive supply of energy to the body of the patient, which leads to an artificial heating of the tumor and the surrounded tissue. The clinical hyperthermic procedures should take into account the oncologic disease and its pattern of organ involvement. There are three different types of hyperthermia: local hyperthermia (LHT), regional hyperthermia (RHT) and part body hyperthermia (PBH). PBH is used to heat regions of the body in case of metastatic disease. I and phase II trials could show that the effects of radiation and chemotherapy can be altered by the simultaneous addition of hyperthermia. Data of trials involving skin metastasis in malignant melanoma, local relapse in breast cancer, tumors of the head and neck with regional lymph node metastasis, as well as trials in colorectal tumors, bladder cancer, pancreatic cancer, cervical cancer and sarcoma are presented. The results of Schlemmer M, et al; shows, that response to treatment can be improved by hyperthermia.(18)

This d'Arsonval Medal acceptance presentation highlights several research themes selected from Dr. Lin's published works, focusing on the microwave portion of the nonionizing electromagnetic spectrum. The topics discussed include investigation of microwave effects on the spontaneous action potentials and membrane resistance of isolated snail neurons, effects on the permeability of blood brain barriers in rats, the phenomenon and interaction mechanism for the microwave auditory effect (the hearing of microwave pulses by animals and humans), the development of miniature catheter antennas for microwave interstitial hyperthermia treatment of cancer, the application of transcatheter microwave ablation for treatment of cardiac arrhythmias, and the use of noninvasive wireless technology for sensing of human vital signs and blood pressure pulse waves. This reviewr concludes with some observations on research and other endeavors in the interdisciplinary field of bioelectromagnetics.(19)

The objetive of Gofri, et al; was to evaluate the effectiveness of combined local bladder hyperthermia and intravesical chemotherapy for the treatment of patients with high-grade (G3) superficial bladder cancer. The patients with G3 bladder tumors (Stage Ta or T1) were treated with combined intravesical chemotherapy with mitomycin-C and local radiofrequency hyperthermia of the bladder wall. They concluded that combined local bladder hyperthermia and intravesical chemotherapy has a beneficial prophylactic effect in patients with G3 superficial bladder cancer. Ablation of high-grade bladder tumors is feasible, achieving a complete response in about three quarters of the patients.(20)

Laptev PI, et al; did a review of a total of 424 patients with cancer of the lips, lingual mucosa, and bottom of the oral cavity were treated using local hyperthermia and CO(2) laser. The best results were attained in patients with the disease stage T1N0M0-T2N0M0: 5-year survival without local relapses and metastases was 43.3-58.5% in this group.(21)

Heat shock protein 70 (Hsp70), a protein induced in cells exposed to sublethal heat shock, is present in all living cells and has been highly conserved during evolution. The aim of the current study of Khoei S, et al; was to determine the role of heat shock proteins in the resistance of prostate carcinoma cell line spheroids to hyperthermia, in samples treated with hyperthermia at 43 degrees C for 120 min, the spheroid cultures expressed a higher level of Hsp70as compared to monolayer culture. Under similar conditions of heat treatment, the spheroids showed more heat resistance than monolayer cultures as judged by the number of colonies that they formed in suspension cultures. The results suggest that cells cultured in multicellular spheroids showed more heat resistance as compared to monolayer cultures by producing higher levels of Hsp70.(22)

To investigate the protective effects and mechanism of heat shock response (HSR) on circulatory collapse induced by hyperthermia. Wang B et al; two experiments were carried out: (1) Protective effects of HSR. (2) Mechanism of effects. They concluded that HSR may induce upregulation of HSP70 and inhibit excessive production of NO in myocardium, thus result in relief of circulatory collapse induced by hyperthermia.(23)

Whole body hyperthermia (WBH) has been used as an adjunct to radio-/chemotherapy in patients with various malignant diseases. Although clear evidence is still missing, it has been hypothesized that an activation of the immune system might contribute to the therapeutic effect of WBH. The aim of Atanackovic D, et al; it was to examine the effect of WBH-CT on the expression of a broad range of activation markers on peripheral blood lymphocytes (PBL), on serum cytokines and intracellular cytokine levels in T cells, and the capacity of these cells to proliferate. Furthermore, the percentage of CD4+ T cells expressing the T cell activation marker CD69 increased nearly two-fold over time, reaching its maximum at 48 h ($P<0.05$). As an additional marker for T cell activation, serum levels of sIL-2R increased markedly ($P<0.01$), reaching maximum levels at the same point in time. Elevated intracellular concentrations of interferon-gamma (IFN-gamma) and/or TNF-alpha in CD8+ T cells were found in 4 out of 5 patients at 24 h post-WBH-CT. Since similar changes were not observed in patients receiving chemotherapy alone, this is the first study to provide evidence for prolonged WBH-CT-induced activation of human T cells.(24)

As an adjuvant to chemotherapy hyperthermia has proven to be successful as a treatment for osteo- and chondrosarcoma patients. Kubista B, et al; investigated whether hyperthermia could increase cellular expression of heat-shock-protein 72 in human osteo- and chondrosarcoma cells and how heat treatment would affect their susceptibility to natural killer cell (NK-cell)-mediated lysis. They found that hyperthermia increases HSP72 expression in osteo- and chondrosarcoma cells and their susceptibility to NK-cell-mediated lysis. These findings may lead to new therapeutic strategies, using hyperthermia to improve immunological defense against chondro- and osteosarcoma cells.(25)

Effects of hyperthermic water bath on selected immune parameters (lymphocyte subpopulations, natural killer (NK) cell counts and their activity) were studied by Blazickova et al; Application of hyperthermic water bath both topical and whole-body) was followed by a significant reduction of relative B lymphocyte counts. Whole-body hyperthermic water bath reduced relative total T lymphocyte counts, increased relative CD8+ T lymphocyte and NK cell counts and increased NK activity. Whole-body hyperthermic bath increased somatotropic hormone (STH) activity; higher relative counts of CD8+ lymphocytes and NK cells were observed. The STH was released in response to local hyperthermic water bath and the NK activity of lymphocytes also increased but their relative counts did not. The results suggest that these increases in CD8+ lymphocyte and NK cell counts are probably dependent on increased STH production. (26)

Fuggett et al; performed experiments to confirm the inhibitory effect of HY (42 degrees C for 1 hour) on natural killer (NK) activity and to evaluate the influence of HY on the generation and cytotoxic activity of interleukin-2 (IL-2)-activated NK cells. They showed that HY profoundly reduced the lytic activity of NK cells and demonstrated that this inhibition was transient and not due to an apoptosis-induced reduction of the number of effector cells. Moreover, the exposure of mononuclear cells to HY before IL-2 stimulation did not affect the generation of IL-2-activated NK cells, whereas, the hyperthermic treatment of IL-2-activated NK cells produced a marked reduction of their cytotoxic activity. The results also showed that the simultaneous exposure of effector and target cells to HY, during the cytotoxicity assay, produced a marked reduction of lytic activity of NK and IL-2-activated NK cells, and that this impairment was specific for effector cells. In this context, heat-exposure of target cells alone, did not substantially modify their susceptibility to lysis induced by either NK or IL-2-activated NK cells. These results add further evidence of HY-induced inhibition of natural cell-mediated immunity, and suggest that, in the course of therapeutic HY, immune response could be significantly altered.(27)

Hu Y, et al; studied the effects of local hyperthermia on primary and metastatic focus. They established an animal tumor model in a mouse by injecting 5 x 10(5) Lewis lung carcinoma cells into the left foot pad. Ten days later, a tumor mass of 10 x 10 mm was seen, and local hyperthermia was performed at 37, 43, 45 and 47 degrees C for 30 minutes. They found, NK activity increased after 43-45 degrees C hyperthermia.

The growth rate and lung metastasis decreased. They concluded that Host immunity is thought to be enhanced by local hyperthermia and plays an important role in eradicating primary tumor and controlling distant metastasis. (28)

Nakayama et al; took two cases of metastatic malignant melanoma of the lower limb who were treated successfully with hyperthermic isolated limb perfusion. Analysis of immunological parameters showed that the number of peripheral CD8+ lymphocytes gradually and constantly increased after the operation, while that of CD4+ lymphocytes transiently increased and then returned to the pre-operative level. Natural killer activity transiently decreased to a slight degree 4 days after the operation and then returned to the pre-operative level 21 days after the operation. These results suggest that hyperthermic isolated limb perfusion with concomitant infusion of carboplatin or beta-interferon is effective in suppressing the growth of metastatic malignant melanomas of the lower limb.(29)

Immune and central nervous system (CNS) interactions are complicated because afferent signals from the immune system to the CNS in response to antigens or infections may elicit an immediate efferent response to the immune system. Conditioning can be used as a tool to take the communication loop apart. In conditioned animals, the conditioned stimulus can be employed later to trigger the site of the association memory located within CNS, and set off the efferent pathway. Conditioning therefore allows one to isolate and identify the potential circuits in the brain that becomes conditioned. We have conditioned a pathway in the brain which can be used to modulate core body temperature (Tc) and natural killer (NK) cell activity. The Tc and NK cell activity are used as readouts to detect the expression of the conditioned response which is taking place in the brain. Since various cytokines (IFN, IL-1 etc) that are produced by antigenic stimulation invariably raise fever, it appears that the immune system could signal the CNS with nonspecific cytokines that activate the hypothalamic-pituitary pathway to modulate core body temperature. These observations infer that the thermoregulatory pathway in the brain becomes conditioned and points to a common pathway of communication in which interferon-beta, prostaglandin E2, CRH and ACTH appear to play a role in modulating both Tc and NK cell activity.(30)

Fujieda et al; determine whether heat-treated thyroid cancer cells augment the susceptibility of target cells to lysis by autologous lymphokine-activated killer cells. The susceptibility of heat-treated thyroid cancer cells to lysis by autologous and allogeneic lymphokine-activated killer cells was significantly greater than that of untreated tumor cells. The mechanism of enhanced susceptibility was unclear. However, the effect depended on de novo protein synthesis, because inhibition of RNA synthesis by dactinomycin completely abolished the heat-enhanced susceptibility of tumor cells. They concluded that Immunotherapy combined with hyperthermia may be useful in management of thyroid cancer.(31)

Murine experiments were undertaken to study the impact of acute and chronic exogenous hyperthermia on the functional activity of natural killers. Single hyperthermia of the animals up to 42 degrees C and thermal shock stages were shown to be followed by suppressed activities of natural killer cells. Daily hyperthermia at 43-44 degrees C for 20 min during 3, 5, and 10 days was characterized by the depressed functional activity of natural killers. Hyperthermia for 20 and 30 days revealed no changes in the activity of natural killer cells. It can be assumed that there is a decrease in antitumor responses of the body in acute hyperthermia and in early chronic hyperthermia.(32)

The therapeutic efficacy of cellular immunotherapy depends not only on the anti-tumor activity of the administered effector cells but also on their ability to gain access to the tumor by extravasation. Although interleukin-8 (IL-8) has been shown to prevent the vascular leak associated with IL-2, it also abrogates the anti-tumor effect of IL-2. Geehan DM, et al; undertook these studies to determine if LHT could abrogate the anti-immunotherapeutic effect of IL-8, since IL-8 inhibits leukocyte adhesion. They found that IL-8 was able to increase the activity (P = .07) of the mice when administered with IL-2. These results suggest that IL-8 may protect the tumor-bearing animal from the systemic toxicity of IL-2, while LHT abrogates the anti-immunotherapeutic effect of IL-8.(33)

Strauch et al; studied the combination of immunotherapy and hyperthermia results in a greater reduction in tumour growth compared to either therapy used alone in a murine subcutaneous tumour model. The mechanism of this beneficial effect may be related to increased trafficking of immune active cells to the tumour-bearing site, an increase in the sensitivity of tumour cells to lysis, or perhaps a local release of cytokines induced by hyperthermia. This study established the efficacy of combined immunotherapy and hyperthermia for the treatment of visceral metastases and provides impetus for the initiation of clinical trials.(34)

Pedersen et al; found that, Natural killer (NK) cells are highly influenced by physical exercise. The possible important mechanisms behind exercise-induced changes in NK cell function are cytokines, hyperthermia, and stress hormones, including catecholamines, growth hormone, cortisol, and beta-endorphins. It is suggested that during the time of immunodepression microorganisms, especially virus, invade the host, whereby infections can be established. However, in those who perform regular moderate exercise the immune system will often be temporarily enhanced and this will protect these from infections.(35)

Yang H, et al; studied cells with natural killer activity (NK), which may play an important role in host defence against tumour cells. The lytic function of NK cells is very sensitive to hyperthermic inactivation. This was accompanied by a greater inhibition (62-77%) of NK lytic activity. Kinetic analysis indicated that MTOC reorientation capacity recovered following incubation at 37 degrees C. These data indicate that NK cells recover NK-specific lytic activity after heat inactivation. Moreover, our study demonstrates that hyperthermia interferes with post-binding MTOC reorientation, and further supports a role for microtubule in secretory processes involved in NK-mediated cytolysis.(36)

Kappel, et al, designed to test the hypothesis that elevations in body temperature of humans induce immunostimulation. The interleukin-2 (IL-2) enhanced natural killer (NK) cell activity (lysis per fixed number of mononuclear cells), as well as the proportion and total number of NK cells (CD16+ cells), increased significantly during hyperthermia compared with control values. The lymphocyte proliferative responses did not differ significantly between hyperthermia and thermoneutral conditions. Induced hyperthermia causes significantly increased serum cortisol, plasma norepinephrine and plasma epinephrine concentrations compared to controls. It is possible that the altered immune functions induced by elevated body temperature can be ascribed to altered composition and function of blood mononuclear cells induced by elevated levels of stress hormones.(37)

Yoshioka et al; studied the effect of in vitro hyperthermia treatment on the immunological function of human peripheral blood mononuclear cells (PBMC) to evaluate the immunosuppressive effect of hyperthermia, which has been successfully used for the treatment of cancer. Both natural killer (NK) activity and phytohaemagglutinin (PHA)-induced blastogenesis were temperature-dependently reduced after the treatment. After the treatment at 44 degrees C, NK activity was only 4.3% and no PHA-induced blastogenesis was observed. The reduced NK activity after the treatment may be in part due to a decreased number of subpopulations of highly active NK cells. Therefore, the possibility of hyperthermia-induced inhibition of the host immune system must be considered when we use hyperthermia clinically for cancer treatment.(38)

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