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Hyperthermia in Cancer Treatment: A Primer

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in the emerging field of hyperthermia.
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CONTENTS

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PREFACE

Although remarkable progress has been made in cancer therapy, many cancers, particularly solid cancers, are still untreatable by conventional therapies such as radiation, immunotherapy, surgery or chemotherapy. This creates the need to improve cancer treatment. Hyperthermia for its synergistic action with the aforementioned modalities may be considered the fifth modality of treatment.

Hyperthermia is defined as a therapy in which tumor temperature is raised to values between 41°C and 45°C by external means. It can be applied locally/regionally or to the whole body depending from the stage of the cancer patients.

For decades hyperthermia has been an area of laboratory investigation with moments of enthusiasm and disappointment, but now there is renewed interest. Its effectiveness as a cancer treatment has been demonstrated by many trials in Europe. These trials have highlighted that hyperthermia improves cancer treatment results while decreasing the side effects of conventional therapies.

Following overviews on hyperthermia physics, this book comprehensively describes the biological rationale for associating hyperthermia with radiation and chemotherapy and the biological and clinical effects of heat on cancerous and normal tissues. Chapters are arranged in three main sections (physical and methodological studies, biologic principles, clinical studies).

The first part devoted to the physical principles underlying heat generation in tumor tissue has been kept to a minimum, so as not to put off clinicians or students. An entire chapter regards thermometry since temperature measurements, or better, thermal dose calculations are clinically critical. Currently no simple methods of temperature measurement inside tumor mass are available. The advent of noninvasive thermometry is warranted; some attempts have been made using ultrasound and magnetic resonance. Unfortunately, these measurements call for skilled teams composed of medical physicists and clinicians. Nanotherapy application with heat is reviewed by an expert in the field.

The interactions of hyperthermia with tumor metabolism and its environment, particularly the effects on angiogenesis and vasculature, are discussed broadly and in depth in the second section. A chapter describes the tumor microenvironment and its manipulation in order to increase thermoresponse.

A specific chapter is devoted to clinical trials with chemotherapy and radiotherapy, offering the opportunity to understand the therapeutic gain of heat. Aspects of tumor biology relevant to this kind of treatment and especially to brain tumors are described with particular attention to their clinical relevance.

The third section of the book deals with the clinical applications of radiofrequency and perfusion hyperthermia; other methods for generating heat such as microwaves or ultrasound have been avoided. Interstitial hyperthermia applications on the liver and antiblastic limb perfusion applications are described by experts in the field.

Whole body hyperthermia treatment is described by two groups of authors that use different modalities of heating.

Taking into account the side effects of various cancer therapies on immunity, we thought it appropriate to evaluate the various therapeutic approaches and interactions of this kind of therapy with immunity. A chapter on fever therapy has been also added, and the reader can understand the specific benefits of the thermal component of fever on the immune response.

The main purpose of the book is clinical, and it must be considered a primer or an update for experts on the matter. One of our purposes is to provide physicists and engineers with information on the biological effects of heat on tumor tissue, aspects not deeply discussed in bioengineering curricula.

We hope this book will be of interest to internists, oncologists and to all physicians involved in the management of cancer patients.

Gian Franco Baronzio
Erich Dieter Hager

INTRODUCTION

Introduction and Brief Historical Notes on Hyperthermia

If knowledge can create problems, it is not through ignorance that we can solve them.
—Isaac Asimov
The art of medicine consists in amusing the patient while nature cures the disease.
—Voltaire (1694-1778)

According to the National Institutes of Health (NIH) hyperthermia (also called thermal therapy or thermotherapy) is defined as a type of cancer treatment in which body tissue is exposed to high temperatures (up to 106°F), to damage and kill cancer cells, or to make cancer cells more sensitive to the effects of radiation and certain anticancer drugs.

Hyperthermia (HT) is used as an adjunct therapy to radiotherapy and/or chemotherapy to increase their effectiveness,[1,2] but hyperthermia alone exhibits both antineoblastic and immunological effects.

For decades hyperthermia has been an area of investigation with moments of excitement and disappointment, but now encouraging clinical results have renewed interest in its clinical application.[3]

Historically, hyperthermia was used many centuries ago by Romans, Greeks and Egyptians to cure breast masses.[1] Indian ayurvedic physicians practiced local and whole body hyperthermia in 3000 BC. The method consisted of at least five stages of oleation, dietary regimens and purgation with locally or whole body heat application, e.g., a poultice of cotton wool or heated stones employed to treat the liver. Whole body hyperthermia (WBHT) was obtained using vapor produced by sprinkling liquids over heated stones, bricks or metal blocks. Many recommendations and simple methods for estimating the quantity of heat delivered have been described.[4]

In 1868 Busch in Germany concluded that fever induced by certain bacteria as erysipelas can cause tumor regression or cure cancer. This was concluded after the observations of a patient with a soft tissue sarcoma of the neck infected by erysipelas.[5] The causative agent (streptococcus) at that time was not identified. Subsequently, in 1891, a young American surgeon named Coley, unaware of Busch's observation, observed a regression of a soft tissue sarcoma in a patient infected by erysipelas. Stunned by the finding, he searched the medical literature and found many publications confirming the same observation.[6,7] Coley initially prepared a culture of streptococci injected at the tumor site with encouraging results. He even noted that the presence of *Serratia marcenscens* could enhance the virulence of streptococci and that a remote injection from the tumor could result equally in tumor regression. After these observations Coley incorporated *Serratia marcenscens*

into the streptococcal vaccine, forming the "Coley's toxin".[7] The intravenous route was the most effective, and a dose of the toxin was considered sufficient only if accompanied by fever (39-40°C). Sustained pyrexia was considered the critical point in tumor regression.[6,7] It was also observed that those who developed the highest fever were most often the ones with the longest survival. Other antitumoral effects not linked to fever are now recognized.[8] The fever and pyrexia inducers are now recognized to be caused by tumor necrosis factor-alpha (TNF-α) and other cytokines.[9]

In the last decade numerous randomized or nonrandomized clinical trials have been conducted.[1,3] Most studies were done in combination with radiotherapy (RT) and chemotherapy, in different order, to obtain a better loco-regional control of superficial tumors. Among these, recurrent and primary breast lesions, head and neck neoplasms and melanoma have been treated with radiotherapy in association with hyperthermia. The thermal enhancement ratio was increased for all cases from 1.4 to about 2. The most important prognostic factors for a complete response were radiation dose, tumor size, minimum thermal dose and temperature. The total number of heat fractionations delivered do not appear to be important, provided that adequate heat is delivered in at least one or two sessions.[10]

Although there are positive clinical trials, oncologists are skeptical about hyperthermia even if hyperthermia is the only therapy able to exploit the unfavorable tumor microenvironment. In fact, within tumors, regions with reduced blood supply, with active anaerobic metabolism and low pH, are the most sensitive to the cytotoxic effects of hyperthermia as compared to radiotherapy or chemotherapy. For larger tumors, acidic-hypoxic environments are the rule. Furthermore, local hyperthermia (LHT) has been demonstrated to induce radiosensitization at temperatures < 42°C, and to increase oxygenation, an issue which would partially explain its radiosensitization effect.[1]

Some trials on esophageal cancers have been done using (triple modality) radiotherapy, hyperthermia, chemotherapy [RT-HT-CH]). The results are encouraging, depending on the disease stage, as two-year survival rates have been observed in the range of 20-30%. Despite this, progression of the disease and relapse are common. In the case of stomach and pancreatic cancers, combined therapy HT + chemotherapy (mitomycin-C, 5-fluorouracil) have been performed with positive effects on survival and on objective complaints.[11]

Interstitial hyperthermia (thermal ablation with RF or laser), has reached good therapeutic targets in terms of clinical results, side effects, limitations and costs. On the wave of these positive results, interstitial hyperthermia is now gaining new fields of applications, e.g., in liver, breast, kidney, bone and lung tumors.

Patients with peritoneal carcinomatosis or sarcomatosis have a poor prognosis even when the disease is confined within the abdominal cavity.[12,13] Different therapies have been proposed, ranging from surgery to intracavitary chemotherapy. Regional perfusion chemotherapy achieves a high intraperitoneal concentration, minimizing systemic toxicity. However, an intraperitoneal route cannot guarantee adequate drug penetration into larger tumors. To overcome this problem, debulking surgery combined with chemotherapy has been proposed.[14] Despite this procedure, the combined treatment has not improved the clinical outcome markedly. Heat has been demonstrated to boost the activity of some antineoblastic drugs (cisplatinum, doxorubicin, mitomycin-C) suggesting that the combination of debulking surgery + chemo-hyperthermia (HIIC) can maximize the antitumor cytotoxic effect.[16] Phase III studies are still in progress. Phase II studies were positive for overall and disease-free survival rates; however randomized clinical trials are necessary to provide a definitive response.[12,13] On the basis of peritoneal chemo-hyperthermia experience, other perfusional hyperthermia techniques have been developed for treating life threatening tumors confined to liver, lung, pleura and limbs. Isolated organ perfusion systems were developed by Creech. Subsequently, the method was adapted for treating various organs with hyperthermia by different authors including Cavaliere in Italy.[17] Perfusional techniques have become standardized and complications have been reduced to a minimum. Approximately 8 to 10% of primary melanomas involve extremities. In this case all the extremities are at risk, but amputation does not cure the disease. To try a definitive cure isolated limb perfusion (ILP) has become the choice. Initially melphalan was identified as the best agent to use with ILP, subsequently it was demonstrated that increased activity was achieved in combination with hyperthermia. Cytokines have also been approved for combination.

Regional hyperthermia + ILP resulted in a response rate between 78 to 83% for melanomas. Based on these results the method was applied to soft tissue sarcomas; melphalan or doxorubicin were used, reaching response rates between 45% and 60%.[11] Recently European investigators have shown that it is possible to reach a complete response rate near the 90% and a longer duration response by adding to melphalan tumor necrosis factor-alpha (TNF-α).[18, 19]

Different trials in Europe and overseas are in progress with TNF-α, and other biological response modifiers (BRMs) such as interleukin-2 (IL-2) and interferon gamma (INF-γ).

Notwithstanding these positive results, Takahashi clearly illustrated the problems that must be resolved to consider hyperthermia clinically relevant. They are: specific apparatus to maintain a stable temperature distribution, cost of therapy, long hospital stay, and clinical know-how to avoid complications. Furthermore the author concluded that "For clinicians to accept hyperthermia as conventional

therapy, more evidence must be drawn from prospective studies, and a definitive evaluation of the prognostic factors is needed".[11]

Insight from earlier clinical trials with hyperthermia indicates:

1. For establishing a hyperthermia clinical trial, quality criteria are needed; these have been collected separately by Overgaard and Nielsen.[21,22]
2. Temperature measurements, or better, thermal dose calculations are critical. This confirms the in vitro studies that have established that thermal cytotoxicity is a function of both temperature and time. The measurement of the thermal dose is the great challenge for the future. Actually no simple clinical methods of temperature acquisition inside tumor mass are available. The advent of noninvasive thermometry is warranted; some attempts have been made using ultrasound and magnetic resonance. Unfortunately, these measurements require skilled teams, composed of physician and clinicians.
3. How many hyperthermic applications are necessary to obtain good clinical results? Animal studies indicate that sometimes only one or two sessions of HT are sufficient. Clinical trials indicate that a single treatment once a week for at least five weeks is necessary but any definitive response has not yet been obtained.

The role of the biological effects of hyperthermia like immunotoxicity, antiangiogenesis, and proteasome inhibition have to be further elucidated. Synergistic effects with antibody targeted therapy are also new, promising aspects in hyperthermia treatment.

In conclusion, better use of the biological basis of hyperthermia, associated with better thermal dosimetry, will permit hyperthermia to become more than an unfulfilled promise.

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SECTION I
Physical Aspects of Hyperthermia

CHAPTER 1

Hyperthermia, Physics, Vector Potential, Electromagnetic Heating: A Primer

Ugo Cerchiari*

Abstract

Heating methodologies of restricted and specific body volumes as means to treat cancer are critically examined from the physical point of view. Difficulties in the application of heating methodologies are considered in relation to the different means giving more space to the means more suitable for modelling. Since the usual approach of electromagnetic heating and of its modelling is difficult, the use of vector potential is suggested and some simple calculations and considerations are presented for electromagnetic field modelling.

Introduction

Heat is a mechanical energy of incoherent nature of small volumes of matter typically of atomic or molecular dimensions. Incoherent here means that velocities of near atoms are randomly directed and in solids represent vibration of those small portions of matter with random amplitudes and random phases. "Random" means that all possible movements (degrees of freedom) are present and share almost same energy. This energy is continuously exchanged among them.

Temperature T is a parameter that is linked to the energy Q by a coefficient C called specific heat $Q = CT$. Thus in a homogeneous sample of matter temperature is a "measure" of heat.

If the temperature of a volume of biological content increases, as a consequence biochemical reactions increase their speed. Initially this speeds up "life," as can be observed in reptiles or also in many species of mammalians, considering temperature and activity. Yet all functions must increase proportionately. In case of an insufficient supply, substrates are quickly consumed, and essential reactions enter in shortage of biological energy and substances and reject metabolites accumulate. These consequences can lead to essential impairment of functions including repair and transport.Thus, in case of stressed biology, heat may be sufficient to increase death rate in cells. These effects become apparent as temperature goes over a definite threshold (42.5°C). Increasing temperature (beyond 45°C) biological molecules, due to the vibrations of their atoms start to suffer new chemical reactions leading to unwanted products. Those modifications in nature of biological molecules (denaturation) further impair the ability of cells and tissues in doing what they normally do performing their functions. Finally a necrosis is induced. These last thermal effects damage both normal tissues as well as cancer. Thus heat may be used to treat cancer if this energy in mainly distributed to tumours, possibly in

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conjunction with drugs and /or radiotherapy and, if raise in temperature is in a limited interval, to avoid death of normal tissue.

Cells killing by hyperthermia have to be evaluated by a special kind of dosimetry. Heat deposition measured by power per gram (SAR) has no significance since only thermal damaging effects due to temperature exposition should be taken into consideration. Dose as "the measure of thermal effects" is a function of temperature, of time and of thermal sensitivity of target tissue that may depend on the presence of substrates and of drugs or previous damage.

Since even thermometry is not easy at the moment, only simple practical rules can be given, derived by very rough considerations. Chemical reactions starts effectively as thermal energy reaches an activation threshold and increase their velocity as temperature rises (roughly doubling their rate every 10°C) but biological chemistry requires that only a class of reactions should be allowed by limiting the temperature of activation of unwanted reactions. Thus useful reactions are supported by complex mechanisms of transport and catalysis as well as feedback regulation to allow working in a limited temperature range. Equally effective as temperature is shortage of substrates, oxygen especially, as it is well known. So it must be expected that this could be the primary parameter to control beyond temperature.

Yet usually temperature is "the" parameter which is controlled and clinical practice suggests that a temperature of 42.5°C should be kept for 4 hours to obtain the same effect of 45°C for ten minutes. In between of the two a working temperature and a practical time of treatment has to be clinically decided mainly in relation of the weight of the region to be heated and blood perfusion.

Various methods have been developed to release heat in tumours having different features:

1. Direct heating by conduction by contact with a heat source:
   a. localized transcutaneous (superficial)
   b. invasive, interstitial and intracavitary
   c. extracorporeal circulation of hot blood in an organ
   d. heating generalized to whole body by conduction from a thermostatic bath
2. Indirect heating by deposition of coherent energy relaxing locally to incoherent energy (heat):
   a. mechanical vibration (ultrasound waves)
   b. low or high frequency electromagnetic fields

All these methods face great difficulties deriving mainly from the complex nature of organs and tissues as regards their not uniform physical properties, geometry and blood flow.

Since the temperature threshold of biological damage and the increase of the damage with temperature are critical it is immediately obvious that to predict or control the temperature distribution in a body region is mandatory. Unfortunately this is a difficult task.

Accepted thermometry requirements are:

1. Overall accuracy < 0.2°C
2. Response time < 4 seconds
3. Sensor size < 2 mm
4. Possibly immunity or no substantial interference with the heating technique

Since energy deposition in tissues as well as cooling by blood flow are difficult to model, a good thermometry control with few exceptions is always needed in clinical practice. Unfortunately not invasive thermometry, that in principle could be attained by microwave radiometry, MRI temperature-dependent signal or electrical impedance tomography, still do not meet the requirements for clinical application.

Thermometry will be treated in more details elsewhere in this book.

As starting sources of Hyperthermia physics we suggest the articles in references 1-4.

Direct Heating

Direct heating is efficiently attained in a range of 10 mm in depth from a heat source covering the lesion with a border in excess of 20 mm. This condition can be met for cutaneous or intracavitary lesions.

Interstitial treatments can be planned with linear heat sources spaced no more than 15 mm apart. Sources are tubes 1.6-2 mm in diameter with turbulent hot water flow or electrically heated probes.

Normal tissue can be partly preserved by thermally insulating probes with low heat conducting coating in case of tubes or by electrical heated probes of suitable length. Temperature control poses no problem with any kind of invasive thermometry combined with sources.

Unfortunately these devices are not commercially available as dedicated systems.

Direct heating as a whole body technique as been used in the past by pyrogenic toxins or heat bath (water and/or air) but it is obviously limited in temperature and was usefully used in combination with other agents. Now could be used as a background temperature control in local heating. Yet the experience suggest that it is a risky treatment.

Regional perfusion by external circulation of hot blood has also been attempted and also this technique has to be considered of difficult execution.

Heating by Ultrasounds

Mechanical oscillations propagate in media and vibration, in contiguous portions of matter, induce a stress due to a difference in phase of local oscillations. During the cycle of stress and relaxation the medium transforms part of the mechanical coherent energy of oscillation (sound) into random movement thus absorbing "sound energy " and transforming it into heat.

The portion of coherent energy transformed into heat is called absorbed energy and the loss in coherent energy is called attenuation.The velocity of sound in soft tissues is around 1500 m/s while in lung is significantly less (1000-600 m/s strongly dependent on inflation) and in bone considerably higher (2000-3500 m/s).Temperature does not affect velocities to much.

Mechanical waves are commonly induced in tissues by discs of piezoelectric materials. Piezoelectric discs have two electrodes on each face and if a voltage is applied across the crystals then mechanical compression or dilatation occurs. A piezoelectric disc (transducer) in contact with a medium acts as an oscillating piston if an oscillating voltage is applied. Thus a compression wave with oscillation in forward and backward direction (longitudinal in respect to the thickness of the disc) is generated. This in principle, what really happens is different, since piezoelectric crystals are sufficiently rigid to have their own oscillating frequencies and modes that are excited by mechanical stress making front face oscillate with not uniform amplitude. These not uniform amplitudes could generate small hot spots in front of crystals. To mitigate this problem the exciting frequency is modulated to mix secondary excitement modes and a bolus of water is placed between the disc and the skin to attenuate secondary (higher) frequencies.

Transducers have dimensions between 3 and 12 cm in diameters driven by a frequency (ν) in the range from 0.5 to 3 MHz (ultrasound US). At these frequencies the wavelength (λ) in soft tissues is between 0.5 to 5 mm generating almost plane waves with little diffraction. Power densities in front of transducers is in mean 0.5 to 2 W/cm^2. At higher power densities oscillation amplitudes can induce "boiling" (cavitation) in the water bolus and bubbles can induce scattering of waves. To avoid cavitation it is necessary to degas the water. Water in front of the disc firstly heated by US can circulate in a cooler and thus provide cooling in the first centimetre of skin.

Let us examine ultrasound waves in a uniform medium to understand some basic properties. A volume, of uniform medium, is excited by a plane transducer T at the left (Fig. 1). In front of T pressure waves are generated in the medium with fronts parallel to the surface of T. A small volume element of cylindrical shape is displaced by the wave from its equilibrium position x of a quantity **A**.

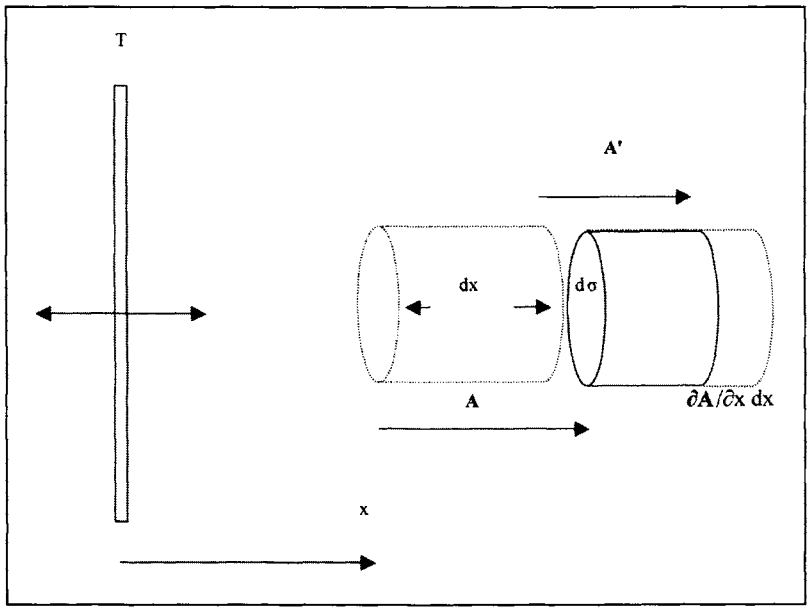

Figure 1. A cylindrical microscopic volume whose base at equilibrium has position x is displaced by pressure of an amount **A**. The opposite base is displaced of **A'**. Cylinder lenght dx is reduced by an amount $\partial\mathbf{A}/\partial x\ dx$.

Displacement is not uniform along x in the volume since pressure wave strains the medium. As a consequence the volume element changes in length of an amount which is:

$$dl = \partial\mathbf{A}/\partial x\ dx$$

This changes the original volume $dV = dx\ d\sigma$ by the quantity:

$$\delta V = dl\ d\sigma = \partial\mathbf{A}/\partial x\ dx\ d\sigma$$

Change in volume modifies internal pressure by an amount dp depending on a coefficient K, characteristic of the medium, called bulk modulus, representing the change of pressure due to the fractional change in volume $\delta V/dV$:

$$dp = K\ \delta V/dV = K\ \partial\mathbf{A}/\partial x\ dx\ d\sigma/(dx\ d\sigma) = K\ \partial\mathbf{A}/\partial x$$

Since the strains before and after the volume element are not equal, pressures as well are not equal, thus moving the volume element. This difference in pressure, indicated by d^2p, depending on the second derivative of **A** is:

$$d^2p = K\ \partial^2\mathbf{A}/\partial x^2\ dx$$

The force acting on the volume element, and effectively moving the element, is the pressure across the area $d\sigma$:

$$df = d^2p\ d\sigma = K\ \partial^2\mathbf{A}/\partial x^2\ d\sigma\ dx$$

The mass dm of the volume element is related to density ρ of the medium by:

$$dm = \rho\ d\sigma\ dx$$

Acceleration of the volume element is $\partial^2\mathbf{A}/\partial t^2$ i.e., the second time derivative of the displacement.

Neglecting at the moment the attenuation of the motion due to the frictional force we may write the equation of motion (f = ma) for the volume element:

$$K\,\partial^2\mathbf{A}/\partial x^2\,d\sigma\,dx = \rho\,d\sigma\,dx\,\partial^2\mathbf{A}/\partial t^2 \text{ or } \partial^2\mathbf{A}/\partial x^2 - \rho/K\,\partial^2\mathbf{A}/\partial t^2 = 0 \quad (1)$$

This equation has the following solution :

$$\mathbf{A} = \mathbf{A}_0 \cos(2\pi(\nu t - x/\lambda)) \quad (2)$$

where ν is the frequency i.e., the number of oscillation made in one seconds at a fixed point and λ is the wave length i.e., the space spanned by an oscillation at a fixed time and $\mathbf{A}_0$ represents the maximum displacement due to the vibration of the transducer.

It is easily seen, substituting expression (2) into eq. (1), that $\lambda\nu$ must be equal to $(K/\rho)^{1/2}$. The solution of eq. (1) represent a simple harmonic wave whose phases (i.e., the argument of the cosine) are constant along planes orthogonal to the direction of propagation x. The crests, where $\cos(2\pi(\nu t - x/\lambda) = 1$ i.e., where the phase is equal to zero, are located where $\nu t - x/\lambda = 0$ and thus move at velocity $c = x/t = \lambda\nu = (K/\rho)^{1/2}$.

Sound is only slightly attenuated in tissues since it travels many λ's.

Disc diameter is considerably larger than λ thus oscillations in the medium can be modelled by a simple exponentially attenuated plane wave whose amplitude of oscillation **A** is given by

$$\mathbf{A}=\mathbf{A}_0\, e^{(-\mu x)} \cos(2\pi(\nu t - x/\lambda)) \quad (3)$$

This expression is a solution of an equation slightly more complex than (1), taking in to account that, besides the elastic force $K\,\partial^2\mathbf{A}/\partial x^2$,during the movement the volume element is also subject to a frictional force proportional to the velocity $\partial\mathbf{A}/\partial x$ and opposite to it i.e., $-\eta\partial\mathbf{A}/\partial t$. The coefficient η is called viscosity.

The new attenuated wave equation is :

$$K\partial^2\mathbf{A}/\partial x^2 - \eta\partial\mathbf{A}/\partial t - \rho\,\partial^2\mathbf{A}/\partial t^2 = 0 \quad (4)$$

The meaning of equation (3) is simply that the amplitude of oscillation decreases exponentially $\mathbf{A}(x)=\mathbf{A}_0\, e^{(-\mu x)}$ giving at a depth x a reduced oscillating amplitude.

Substituting expression (3) into eq. (4) it is easily found that the conditions that allow to use (3) as a solution of eq. (4) are:

$$K(\mu^2 - (2\pi/\lambda)^2) + \rho(2\pi\nu)^2 = 0 \quad \text{and} \quad \mu = \eta\nu\lambda/K = \eta c/K \quad (5)$$

Since the frictional coefficient η is very little, in relation to K, it may be considered zero in the second condition (5). This gives $\mu = 0$, i.e., the exponential factor $e^{(-\mu x)}$ is constant and equal to 1 as in eq. (2). The first condition (5) becomes $K(2\pi/\lambda)^2 = \rho(2\pi\nu)^2$ corresponding to the previous condition $\lambda\nu = (K/\rho)^{1/2}$ for the velocity.

For this reason, and for the great approximations implied in treating biological samples, the velocity c is considered $c = (K/\rho)^{1/2}$.

Parameters in relations (5) depend on physics and technology: ν is chosen by technology, K is very high and η is experimentally found dependent on ν as follows $\eta = \eta_t\nu^n$ with n in the range 1 to 2. The exponent n and the coefficient η_t depend on tissue.

Usually μ is of greater practical use then viscosity η, thus the previous discussion leads to the consideration that :

$$\mu = \mu_t\,\nu^n \quad \text{where } \mu_t = \eta_t c/K.$$

The usefulness of equation (3) depends only on the fact that it gives the evaluation of attenuation in the medium but is not useful in reasoning locally where attenuation may be neglected and local values of energy, amplitudes and power may be considered to depend on local amplitude of oscillation given by $\mathbf{A}(x)=\mathbf{A}_0\, e^{(-\mu x)}$

For instance local energy may be easily calculated from the fact that the oscillation energy of a volume element is all in kinetic form when velocity is at maximum and since, from eq. (2), velocity is:

$$\partial \mathbf{A}/\partial t = -2\pi\nu\, \mathbf{A}(x)\sin(2\pi(\nu t - x/\lambda))$$

the maximum volume velocity is $2\pi\nu\, \mathbf{A}(x)$. Kinetic energy of the unit volume element (energy density) is one half of the product of the mass by the square of velocity. Thus local energy density is:

$$E = \rho/2\,(2\pi\nu\, \mathbf{A}(x))^2 = 2\rho\pi^2\nu^2\, \mathbf{A}_0^2\, e^{(-2\mu x)} \qquad (6)$$

From eq. (6) it easily seen that energy density decreases with depth by a factor of $e^{(-2\mu x)}$

For this reason the energy absorbed in the volume in the unit time (Absorbed Power Density) is the difference of energy between two near points i.e., (the x differential of (6) divided by propagation time $dt = dx/c$ (the time that energy takes to travel dx.) i.e.,:

$$APD = dE/dx\; c/dx = -4\, c\mu\rho\pi^2\nu^2\, \mathbf{A}_0^2\, e^{(-2\mu x)} = -4\, c\mu\rho\pi^2\nu^2\, \mathbf{A}(x)^2 \qquad (7)$$

Firstly equations (6) and (7) show that local energy and APD are proportional to the square of local amplitude.

APD is the power density absorbed in the unit volume, that is only a fraction of the power (which is called intensity) transmitted to the unit volume and there present.

Another quantity, often used, related to the APD is the Specific Absorption Rate (SAR) that refers the absorbed power to the mass of the unit volume and thus is related to APD by:

$$SAR = APD/\rho \qquad (8)$$

Considering eq. (3) and eq. (7) it is evident that what firstly matters in relation to energy deposition are the exponential factors $e^{(-\mu x)}$ and $e^{(-2\mu x)}$.

When the depth x equals the length $1/\mu$, the wave has an amplitude $\mathbf{A}$ reduced of a factor $1/e$ (i.e., one third or 36.8%) of the input amplitude $\mathbf{A}_0$. Usually μ is quoted in Np (Nepers) by metre yet to be intuitive it is interesting to consider that the value of $1/\mu$ ranges between 12 cm and 1.2 cm in soft tissues if frequency varies between 0.5 to 5 MHz.

Attenuation in bone is much higher i.e., 3 - 0.1 cm for ν in the same range between 0.5 to 5 MHz.

As may be suspected by the reduction by a factor of 10 of $1/\mu$ related to a rise in frequency of factor of 10, attenuation increases roughly linearly with frequency in soft tissues and with the square of frequency in bone.

Passing from a medium to another waves change velocity, direction and amplitude and can be partly reflected at the interface. To understand what happens it is easier not to consider the interaction at the interface but to examine the behaviour of waves few wave lengths from it. Frequency of oscillation can not change but wave velocity is different in the two media.

To start and to clarify some ideas it is useful to do some simple considerations regarding wave fronts. A preview of wave evolution may be attained according to Huygens principle: considering each point of the medium as a source of a spherical wave inflating at the velocity of the perturbation, the envelope of the spherical waves gives the new wave front with the appropriate phase.

By this principle it is possible to model the transmitted and reflected wave fronts considering every point at the interface as generating a spherical wave at the instant that it is interested by the impinging wave front

The velocities v_1 of incoming and reflected waves are equal since the medium is the same. The transmitted wave in medium 2 has a velocity v_2. For this reason the transmitted wave front changes direction ($v_2 > v_1$ in Fig. 2). In Figure 2 it is represented the evolution of a wave front at time t_1 and at time $t_2 > t_1$.

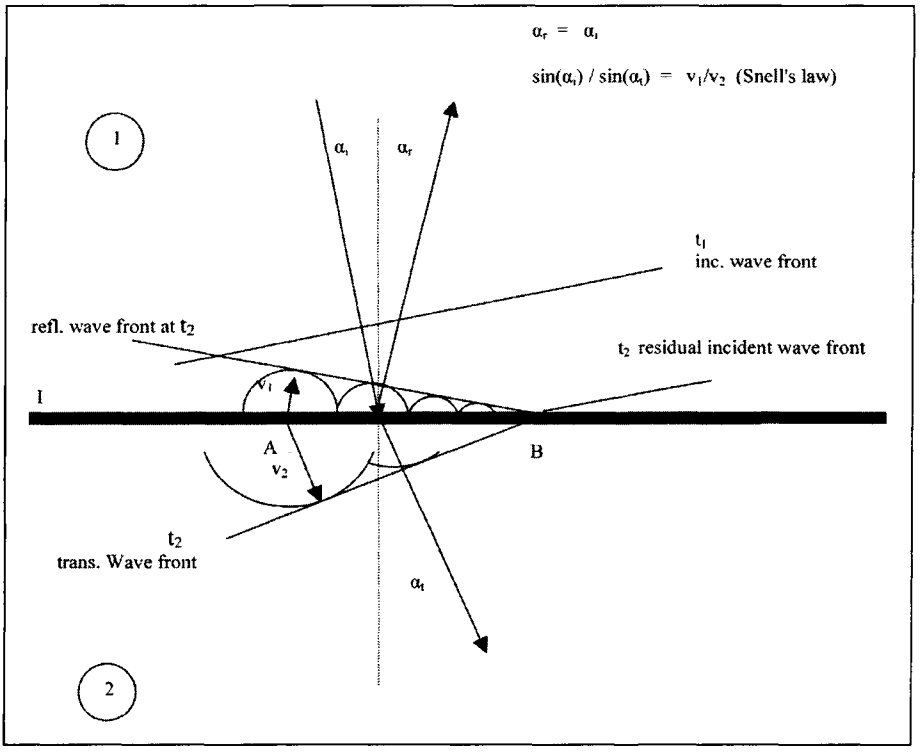

Figure 2. The incident wave front at time t_1 with incidence angle α_i travels against the interface I between two media. At time t_2 wave front is partly reflected with reflection angle α_r and partly transmitted with transmission angle α_t. Transmission angle and incidence angle are related by Snell's law since wave fronts move with different velocities in the two media. Reflection angle α_r is equal to α_i since in the same medium velocity is the same.

At time t_2 the wave front is represented with a reflected and a transmitted front at an interface I and a residual incident front yet to be split.

As the intersection of the front of the wave with the interface I moves from A to B, the wave front splits into one reflected and one transmitted wave front. If the intersection takes a unit of time to travel the length AB then $v_1 = AB \sin(\alpha_i)$ and $v_2 = AB \sin(\alpha_t)$. Thus

$$\sin(\alpha_i)/\sin(\alpha_t) = v_1/v_2$$

If $\alpha_t = \pi/2$ then $\sin(\alpha_t)=1$ and $\sin(\alpha_i) = v_1/v_2$, thus if the angle $\alpha_i > \arcsin(v_1/v_2)$ there is no transmitted wave since "also" the transmitted wave is reflected back.

Changing medium, waves change velocity, amplitude, direction and, keeping frequency obviously unaltered, change wavelength. The easiest way to understand these changes is to consider those parameters that remain unchanged i.e., momentum and energy. Mechanical momentum of impinging wave is conserved and thus must be equal to the sum of the two momenta of reflected and transmitted waves.

Momentum is the product of mass by velocity of a small volume. This quantity is partly transmitted and partly reflected.

The velocity of the volume element is given by the time derivative $\partial \mathbf{A}/\partial t$ in each medium.

Neglecting attenuation, as not interesting in the short range, and thus using solution (2) we have:

$$\partial \mathbf{A}/\partial t = -2\pi\nu \mathbf{A} \sin (2\pi(\nu t - x/\lambda_i)$$

where the index i has value 1 or 2 according to the medium.

This velocity, that incidentally is not the phase velocity of the waves but is the velocity of the volume element of the oscillating material, is different in each medium. The velocity of the volume changes also in amplitude and direction (sign) during time since the factor sin $(2\pi(\nu t - x/\lambda_i)$ changes as time elapses.

Yet the balance of the momentum conservation must hold instantaneously during the oscillation. This fact has two important consequences. The first is that oscillation at the interface in the two media must be in phase and the second is that the only thing that matters is the instantaneous relation among $\mathbf{A}_{1,inc}$, $\mathbf{A}_{1,ref}$, $\mathbf{A}_{2,trasm}$ i.e., the amplitudes of oscillation in media 1 and 2 for the incident, reflected and transmitted waves. The factor sin $(2\pi(\nu t - x/\lambda_i)$ may be neglected since all waves are in phase.

The mass to be taken into account during the exchange of momentum between the two media is obviously the mass of a volume of length proportional to the wavelength. In fact, during a period, a volume of length λ_i is interested by the exchange of momentum at the interface.

Thus we may write the following momentum conservation equation:

$$\nu\lambda_1\rho_1 \, d\sigma \, dt \, \mathbf{A}_{1,inc} = \nu\lambda_1\rho_1 \, d\sigma \, dt \, \mathbf{A}_{1,ref} + \nu\lambda_2\rho_2 \, d\sigma \, dt \, \mathbf{A}_{2,trasm}$$

where $\nu\lambda_1\rho_1 \, d\sigma \, dt = v_1 \, \rho_1 \, d\sigma \, dt$ is the mass of a volume of density ρ_1 of length v_1 dt and section $d\sigma$.The **A**'s are the amplitudes that we have seen are proportional to the velocities. Simplifying and taking into account that the product $v_i \, \rho_i$ is called acoustic impedance and it is indicated by Z_i we have:

$$Z_1 \mathbf{A}_{1,inc} = Z_1 \mathbf{A}_{1,ref} + Z_2 \mathbf{A}_{2,trasm} \qquad (9)$$

(incidentally note that $Z = v \, \rho \, d\sigma \, dt$ is also the mass of the interested volumes)

This is a vector equation since the displacement **A** is a vector. Thus considering a wave impinging orthogonally on the interface line (wave front parallel to it) we obtain for the amplitudes:

$$Z_1 A_{1,inc} = - Z_1 A_{1,ref} + Z_2 A_{2,trasm}$$

Now to conclude the evaluation of transmitted and reflected amplitudes we may use energy conservation.

The kinetic energy of the same volume element is conserved as kinetic energy of the two volume element receiving reflected and transmitted energy. Since kinetic energy is $mv^2/2$ and Z_1,Z_2 are the masses of these volumes and amplitudes are proportional to velocities we may write:

$$Z_1 A^2_{1,inc}/2 = Z_1 A^2_{1,ref}/2 + Z_2 A^2_{2,trasm}/2$$

these relations after some simple calculations lead to the following relations for the absolute amplitudes :

$$A_{1,ref} = (Z_2 - Z_1)/(Z_2 + Z_1) \, A_{1,inc} \qquad (10')$$

$$A_{2,trasm} = 2 \, Z_1/(Z_2 + Z_1) \, A_{1,inc} \qquad (10'')$$

Or calling Γ the reflection coefficient $((Z_2 - Z_1)/(Z_2 + Z_1))^2$

$$A_{1,ref} = \Gamma^{1/2} \, A_{1,inc} \qquad (10')$$

$$A_{2,trasm} = (1 - \Gamma^{1/2}) \, A_{1,inc} \qquad (10'')$$

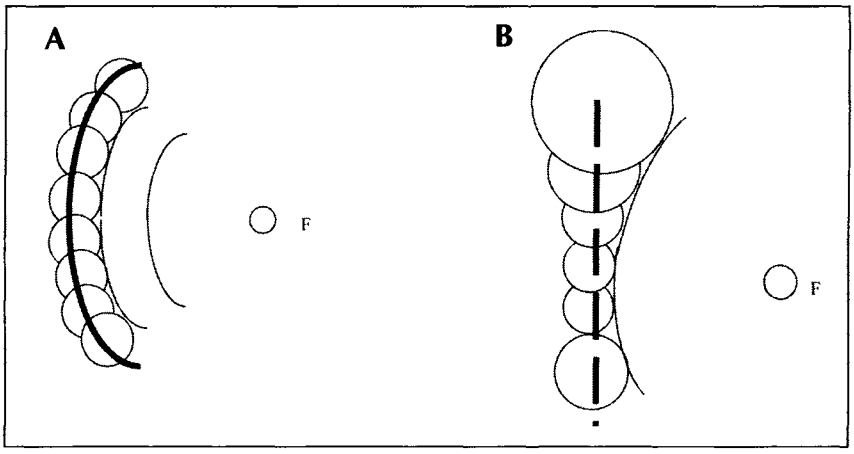

Figure 3. A) A spherical transducer can focus waves reducing problems related to scattering and diffusion. B) An array of transducers, acted with suitable phases, can do the same and can also slightly scan the treatment volume

Since intensities are proportional to the square of the amplitudes, reflected energy is proportional to Γ.

If we consider the following values of density and velocity we can evaluate the percent of power reflected for waves at the interface from soft tissues to bone or lung:

Density of soft tissue will be considered 1 g/cm^3 and sound velocity 1.5 10^5 cm/s thus we have:

	Density	**Sound Velocity**	**Γ%**
Cortical bone	2 g/cm^3	3 10^5 cm/s	30%
Lung	0.3 g/cm^3	0.5 10^5 cm/s	80%

From these evaluations follows that lung is practically not penetrable as well as gas bubbles in the bowel bone also presents great difficulties.

Ultrasound waves can be focused if a spherical wave front is created as can be easily understood applying repeatedly the Huygens principle. By this means an imploding wave can be focused nearly in a volume of dimension of a wavelength if the medium is homogeneous (Fig. 3A). The trick is based on the arrival in phase of all portions of the wave front to the same point F.

An imploding spherical wave may be obtained distributing a set of transducers on a spherical surface and acting them in phase. This is a very effective mean to obtain a disruptive force at F as it is used to destroy renal calculi. Fortunately this approach is not necessary for hyperthermia since is not easy to drive transducers to obtain an arrival in phase at F through different paths in different media.

To obtain hyperthermia at the point F, leaving surrounding tissues relatively cold, it is sufficient to send waves through different paths controlling that F is in the path for each beam and, preferably to avoid interference, acting each transducer during different time intervals.

A spherical imploding wave front may be useful to reduce attenuation due to diffraction and scattering. Since direction and penetration of energy depends on the shape of wave fronts is useful to produce wave fronts with suitable shapes.

The most effective way to obtain a wave front with a variable shape is to assemble a set of transducers acting them with designed phases. This possibility is illustrated in Figure 3B where a plane array is excited adding a suitable time delay to the central elements in respect to the