1. The Cologne Model

The ***Cologne Model*** is a novel and creative approach in the treatment of cancer patients. In the ***Cologne Model***, traditional academic (western) medicine is combined with new therapies, which have a sound scientific basis but are not standard of therapy yet. Therefore, therapeutic interventions and their outcome, including changes in quality of life of all patients, who are treated according to the ***Cologne Model***, will be uniformly documented on a regular basis. In this way, efficacy can be evaluated and therapy modalities can be adjusted. Under the direction of Robert W. Gorter, MD, PhD., documentation and evaluation of all data will be conducted by the International Institute for Oncological and Immunological Research in Cologne, and with its collaborating centers.

Although cancers are various and individual, the available anti-cancer therapies tend to be standardized and seldom address the unique characteristics of a patient's particular tumour. For the most part, these therapies work like carpet bombing: the target is sometimes hit, but often it is not or only to a certain degree, because cancerous cells tend to be well-armoured against attacks, and, in any case, the therapies do considerable collateral damage to normal tissue.

For the same reason that the behaviour of wildlife in captivity may tell one more about captivity than about wildlife, it is difficult to test anti-cancer drugs in a petri dish. To get a better sense of a cancer's real vulnerabilities, you need to have the cells grow as a tumour in an animal, or even better, in a human. The same holds true for the functioning of the immune system. One can take blood samples and count, for instance, numbers and percentages of T-lymphocytes, and correlate numbers with function. But to study the function of T-lymphocytes, the researcher should observe the T-lymphocyte directly when it unfolds its immunocompetent function in the tissue of the organs *in situ*. Therefore, in the ***Cologne Model***, not only immunocompetent cells will be counted and identified through surface markers, but also function tests will be conducted to document cell function and possible improvement of function during and after therapy.

Other treatment modalities will target "*life style changes*". Attention will be paid to nutrition, and possible supplementation with vitamins (anti-oxidants) and trace elements. Other life style changes might include increased physical activities, like bicycling and walking (jogging), and exercise under guidance of an instructor. Adjacent to and in collaboration with the clinic, there is a well-equipped fitness center, where patients can receive expert instruction how to increase adequately their physical fitness through various forms of exercise.

Because of thorough clinical research in the field of *psycho-neuro-immunology* over the last fifteen years, there is no doubt, that there is a delicate but powerful interaction between the functioning of the psyche, or soul, the brain and the immune system. Therefore, it is of utmost importance, that a patient, who has been diagnosed with cancer, or any other life-threatening disease, will be supported in coping with his situation and through social and psychological support from specialized counsellors and psychotherapists. Supportive measurements are participation in support groups, biography workshops, curative eurythmy, art therapy, etc.

In conclusion, one can say, that the ***Cologne Model*** is new and very innovative, as it integrates traditional western academic medicine with novel therapies, paying significant attention to all the needs of the patient, *and* the characteristics of the tumour itself. In addition, all of these therapies have a sound scientific basis, and sufficient clinical experience has been collected to guarantee little to no side effects, and a well-founded hope for a good response to therapy. Good examples of the approach in the ***Cologne Model*** are the treatments with ***dendritic cells***, ***hyperthermia***, ***thymus peptides***, ***Viscum album, procaine-bicarbonate infusions, orthomolecular medicine and improvement of intestinal mucosa and flora***.

2. DENDRITIC CELL THERAPY

2.1. Introduction

Dendritic cells (DC) belong to the group of antigen-presenting cells (APC). One of the first functions discovered of DC was the very important role they play in the activation of specific immune responses against pathogens. Because of this function, they are often called “nature’s adjuvant”. In recent years, through increasing understanding of the role of DC in the immune system, new areas of clinical application were discovered and conducted. One example may be the improved immune response in vaccination of non-responders. Very recently, the possible role of DC in the biological immune response against malignancies (solid tumours) was discovered and clinically investigated.

DC’s form a complex network of APC within the organism (1). In early stages of differentiation, in skin and mucosa, DC have been described as so-called Cells of Langerhans (CL). CL function as perceivers and incorporation of, for instance, viral and bacterial antigens (Ag), and toxins. After perception of an Ag, CL are activated by local inflammatory signals (through the production of certain cytokines, including IL-2 and Il-6), and wander mainly through the lymphatic system, and to a certain degree through the blood flow, to the secondary lymph nodes. Here, as fully differentiated, so-called inter-digitating dendritic cells (IDC), CL settle in the T-cell areas and activate T-cells antigen specific. The function of DC is the transportation of Ag from the location of infection to the secondary lymph nodes, where the specific immune response against the Ag and toxins is orchestrated. Through transportation of Ag by DC to the lymph nodes, it is made easier for T-cells to come into contact with the Ag, as non-activated T-cells circulate through the peripheral lymph system several times during a 24-hour period. After being activated by DC, T-cells change their wander pattern, and become effector cells at the location of infection. As cytotoxic T-cells, they destroy infected cells in the body, and, interestingly, also tumour cells. As T-helper cells of the TH-1 type, they stimulate macrophages in their phagocytic and bactericide activities, by producing inflammatory mediators, to eradicate intra-cellular pathogens, like tuberculosis bacteria. As TH-2 cells, they support the humoral immune response by activating the anti-body producing B-cells.

APC play an important role in recruiting antigen-specific T-cells to adapt properly the immune response. Usually, T-cells by themselves do not recognize Ag. APC have to prepare the recognition of Ag. This means, that within the APC, the (specific) Ag is dissected into much smaller peptides, and bound to the major histiocompatibilty complex class I (MHC-I). Afterwards, this MHC-I is presented at the surface of the cell membrane. Only then, T-cells are able to perceive the complex between the MHC-I molecule and the Ag peptide. This leads to the activation of the resting T-cells. In the periphery of the body CL are specialized in Ag recognition and Ag processing, but still have little potential for activation of resting T-cells. After their wandering to the secondary lymph nodes, and maturation into IDC, the process is reversed. Now, the IDC have lost the ability to recognize and process the Ag almost completely. In stead, IDC, which incorporated the Ag and presented the Ag on the cell surface in its CL stage, are now able to activate resting T-cells. Thus, within the lymph node, IDC guarantee that a most accurate picture is transmitted to the T-cells about the nature and the characteristics of the infection in the periphery. The specific capability of DC to activate naïve T-cells can be used immune therapies, like in cancer. The purpose of our clinical and research activities will be, to sensitise DC for tumour-specific Ag. Thus, given back to the cancer patient through an infusion (as a "cellular vaccine"), in this way specifically-activated T-cells of the patient will be able to eliminate tumour cells and pathogens, including chronic viral infections, like hepatitis C, human papilloma virus (HPV) in persistent cervix dysplasia, and HIV. Recently, it was found, that pre-loaded DC with human immunodeficiency virus type 1 (HIV-1) provoked strong responses from CD8+ T-lymphocytes of late-stage HIV-1 infected individuals. These responses were enhanced under application of gamma-interferon and interleukin-2, strongly suggesting, that DC of HIV-1 positives can be engineered to evoke a stronger anti-HIV-1 CD8+ T-lymphocyte reactivity as a strategy to augment anti-retroviral therapy (10).

2.2. Production and Differentiation of Human Dendritic Cells *in vitro*

DC are spread out throughout the body and are very difficult to isolate. In addition, DC lose their capability for mitosis in their CL and IDC stage. Therefore, even after isolation of DC, no further cell replication is possible. Through years of intensive research by several groups of researchers, like ours, ways have been developed to make DC out of omnipotent peripheral blood stem cells (CD 34+ cells) or peripheral blood progenitor cells (PBPC). Alternatively, monocytes from peripheral blood can be used initially to produce DC in very large quantities by exposing them to GM-CSF, IL-4, TNF-alpha and other cytokines (2-8). Since monocytes are available in large quantities, in the concept of the ***Cologne Model***, we will harvest monocytes from small amounts of peripheral blood taken from the patient and develop them into active DC in this way.

DC are pivotal regulators of immune reactivity and immune tolerance. The observation that DC can recruit naïve T-cells has invigorated cancer immunology and stimulated clinical trials of DC in immunotherapy. However, variables inherent in preparation and use of dendritic cell grafts remain to be tested. Clinical trials with dendritic cell vaccines in myelogenous leukaemia are ongoing (11).

2.3. Sensibilisation of Newly Produced DC with Tumour-Specific Peptides (Ag)

Ag can be introduced into the DC as DNA, which is transcribed and translated by the DC themselves. This foreign protein is then broken down and eliminated by the regular cell metabolism. The peptides, produced in this way, are bound to MHC molecules and presented on the cell membrane surface. In this way, CD8+ cytotoxic T-cells are activated. Activated CD8+ T-cells play an important role in the immune response against tumour cells.

Lysates of pathogens and tumour-specific Ag can be used to sensitise DC. But most Ag presented in this way to DC are not metabolised in the cytoplasm but in the endosomes. Therefore, these peptides are mainly bound to the major histiocompatibility complex class II (MHC-II) molecules, which initiates mainly the activation of CD4+ T-cells. This effect is advantageous in immune responses to infectious Ag and in immunization of non-responder. However, in the treatment of tumour patients, the TH-1 response with its cytotoxic activation is most wanted. Therefore, incubating DC with proteins and lysates as a form of Ag presentation, is not optimal.

Recently, it was shown, that extra-cellular proteins and heat-shock proteins have additional value to enhance the TH-1 type cytotoxic CD8+ T-cell responses. This is an important observation for the development of new treatments of oncological patients. In the ***Cologne Model***, therefore, in addition, hyperthermia is performed in the care of cancer patients.

DC's are used which have been exposed to tumour-specific Ag, which are directly bound to the MHC-I molecule. In this way, one can circumvent the usual route of Ag incorporation and processing and make sure, that the TH-1 response is dominant.

In this way, *in vitro* differentiated and with tumour-specific Ag DC were tested very successfully in animal settings. Tumour regression was seen in most animals.

In the ***Cologne Model***, the patient comes to the clinic for a blood draw (50 ml) at day 1. Our own laboratory processes the blood and monocytes are harvested, and, in a six-day period, changed into DC. Then, if tumour tissue is available, the DC are exposed to the specific cancer antigen of the patient. Then, these sensitised and programmed DC's are re-infused into the patient on day 7. It is recommended, that the patient undergoes an infusion (vaccination) with DC at least six times. Usually, there is a four-week interval between two DC infusions.

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3. WARMTH ORGANISATION AND DISEASE

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

3.1. Introduction

During the evolution of vertebrae, from fish to amphibians, from birds to mammals, one can observe the development of a "warmth organism", or "warmth organisation", which becomes gradually independent from temperatures of the surroundings. In humans, the regulation of body temperature is most developed. Especially in man, 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 of augmentation of maintaining a stabile 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 18.00 and 6.00. o'clock. The amplitude is usually around 0,6 degrees 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 inhibited (1). Therefore, in the ***Cologne Model***, patients will undergo therapeutic interventions to improve both his circadian rhythm and its amplitude, and the maintenance of a stabile core temperature.

3.2. 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 - & 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, and support 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 and the warmth is then spread throughout the body, causing the core temperature to increase.

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 through a rectal thermometer *in situ*. In addition, blood pressure and heart function through an electrocardiogram and an capillary pulse monitor, are monitored continuously. 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 40.0 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*.

3.3. 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.

3.4. Hyperthermia and the Endocrine System

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

Axis pituitary gland – supra-renal 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 till 38.5 C. is not contra-indicated.

Pancreas

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

3.4. Hyperthermia and the Immune System

Since there are intimate interactions between the endocrine system, the nerve-sense system and the immune system (as well-documented in the area of the psycho-neuro-immunology), the effects of hyperthermia on the immune system are many (2). 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 immuno-globulins.

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 (3). Recently, it was well documented that hyperthermia activates compartmental shifting and homing of lymphocytes as well.

In the ***Cologne Model***, patients will undergo total body hyperthermia. Over a period of about two hours, the core body temperature will be increased to about 40 degrees 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.

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4. *VISCUM ALBUM L.* THERAPY

4.1. Introduction

Viscum album (European mistletoe) has been used for medical indications for several centuries. Hildegard von Bingen (….-….) gives several indications for the (oral) use of Viscum album. In the beginning of the 20th century, it was Rudolf Steiner (1861 –1925), who suggested the *parenteral* use of Viscum album in the treatment of cancer patients. Therefore, since 1923, Viscum album has been used and initially studied in the field of oncology. In the last decade of the 20th century, Viscum album, as an immunomodulator, has also been clinically studied in chronic viral infections like in HIV/AIDS, Human Papilloma Virus (HPV) infection in women with cervix dysplasia, and hepatitis C (HCV) infection (1-3).

It is well known, that the extracts of European mistletoe (Viscum album Loranthaceae) has a variety of biological activities such as cytokine production from immune-related cells (1-3), enhancement of natural killer (NK) cell activity (1, 4-6), and immunoadjuvant activity (7-9).

4.2. *Viscum album* and immunomodulation

The immunomodulating and anti-cancer activities of Viscum are caused by biologically active components like lectins (glucoproteins), viscotoxins, alkaloids and polysaccharides (5, 10-12). Especially the mistletoe lectines (ML) have significant activities and therefore, have been studied most intensively (13-15). There have been identified three main groups of lectins: lectin I (ML-I) has an affinity for D-galactose (D-Gal), lectin III (ML-III) for N-acetyl-galactoseamine (GalNAc), and lectin II (ML-II) for both sugars. Among the three lectins, ML-I is most well studied, so that its anti-tumour and immunomodulating activities are well recognized (17, 18). The modes of action of the various components of *Viscum album* have been well summarized and discussed by Fischer (19).

Von Laue has documented, that during parenteral *Viscum album* therapy, there is a positive correlation between the total mistletoe lectin content and the production of anti-ML-I-IgG antibodies (20). Subclasses of anti-ML-I-IgG antibodies can indicate whether a *Viscum album* therapy leads to an activation of Th-I lymphocytes (through production of IgG1 or/and eventually IgG3) or to an activation of Th-2 lymphocytes (through production of IgG2 or/and IgG4) (20).

Usually, through immune stimulation and immunomodulation with *Viscum album*, a Th-1 response is initiated. Through this pathway, a cytokine-dependent *cytotoxity* is provoked, which plays an important role in the natural defence mechanisms against tumour cells. A Th-2 response provokes the production of IL-4, IL-5, IL-10, etc., and thus, B cells increase their production of IgG2 and IgG4. The cytotoxity thus created, is (tumour) antigen-specific, and exhibits a direct lysis of tumour cells.

Therefore, monitoring of IgG subclasses during a *Viscum album* therapy is a very meaningful way to monitor and optimise therapeutic interventions.

In addition, in the early phases of a *Viscum album* therapy, eosinophilia is considered to be a positive phenomenon, and positively related to a partial or complete response in cancer patients.

4.3. Viscum album and circadian rhythms

In general, growing older makes the circadian rhythm of the core temperature, and its amplitude more and more rigid and flat.

In cancer patients, the circadian rhythm of the core temperature and its amplitude, have become significantly hampered. Usually, the core temperature is lowered by about 0,6 degrees C. In addition, the amplitude is flattened. The delicate interaction between the core- and peripheral temperature to maintain a stabile core temperature is also inhibited (21). Therefore, one could say, that the cancer patient grows "old" more rapidly. Parenteral administration of *Viscum album* will usually improve these functions significantly (21, 23). In other words, *Viscum album* juvinates the above described circadian rhythm and so, the warmth organisation.

Thus, in the ***Cologne Model***, *Viscum album* is used to improve effectively T-cell function and the functioning of the warmth organisation of the patient

Recently, pre-clinical and clinical studies have been conducted with the Korean mistletoe (*Viscum coloratum*). Compared to the European mistletoe, very similar activities of the Korean mistletoe in animal models have been documented (22).

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5. THYMUS

5.1. Introduction

Currently, many biological response modifiers (BRM) have been identified. Examples are interleukins and cytokines. Also, the thymus plays an important role in the overall immunomodulation. One could say, that the thymus is the "brain" of the immune system.
In 1560, Andrea Vesalus made a first description of the thymus but it took almost four centuries until in 1936, Hammar suspected that the thymus plays an important role in the immune system after birth. Today, the thymus is considered to have a key function in the development and function of the immune system and the biological defence mechanisms against cancer and chronically infected cells.

5.2. Thymus and its effects on the immune system and lymphatic tissue

Thymic tissue is responsible for selected transformation of precursor cells into different T-cells, i.e. helper (CD4+) T-lymphocytes, which aid in the differentiation of other lymphocytes, killer cells (NK cells) cytotoxic cells and suppressor (CD8+) T-lymphocytes (1-3). Having been released into the blood stream, intestinal and peripheral tissues, the lymphocytes are characterized by well-defined antigens or activation markers on their surface. Their activities are extra thymic.

The thymus is directly innervated and its role in the interaction between the immune system and the neuroendocrinal systems can therefore be understood.

In newborn mice, thymectomy causes a significant change and decrease of lymphatic tissue and a hypofunction of the Reticulo-Endothelial System (RES). In addition, the maturation of T-dependent lymphocytes is severely hampered, or even made impossible.

The thymus produces a variety of substances, including thymus-specific enzymes, -proteins, -peptides and -steroids, which all have both central and peripheral activities. Thymus peptides have a molecular weight of about 300 - 100,000 Dalton. Up to now, some peptide fractions have been isolated and identified, mainly from the thymus glands of young calves, or foetus.

Thymus peptides also play an important role in the development, maturation, differentiation and activation of T-lymphocytes. In addition, thymus peptides enhance proliferation of precursors of lymphoid cells in bone marrow, and their maturation into T-lymphocytes (1-3).

5.3. Thymus and its effects on haematopoietic factors

There is a delicate interaction between the thymus and the active bone marrow. There is a direct and positive correlation between hypofunction of the thymus and the decline of production of colony stimulating factors (CSF). Therefore, in cases where there is insufficient production of CSF, the therapeutic application of thymus peptides can be helpful.

5.4. Clinical applications of thymus peptides

One prospective randomised study in patients with malignant melanoma, thymus peptides caused an increased tumour-free period, a longer survival time and increased quality of life (4).

One prospective, randomised study in intermediate- and high-grade Non-Hodgkin's lymphoma, patients were treated with thymus peptides in addition to standard chemotherapy. The treated patients tolerated thymus peptides quite well and had a significantly higher complete response rate than those patients who did not receive thymus peptides (5).

One prospective, randomised study in patients undergoing colorectal surgery showed, that the patients, who received thymus peptides in addition to Cefotetan, did significantly better in lowering the rate of abdominal abscesses and upper respiratory tract infections (6).

One prospective, randomised study in women with advanced breast cancer could document, that those women, receiving thymus peptides in addition to their chemotherapy regimen, tolerated the chemotherapy significantly better and reduced the rate of secondary infections (7,8).

One prospective, randomised study in breast cancer patients showed that thymus peptides protect the bone marrow functions against the haematological toxicities and recovery during and after high dose of Mitoxantrone (9).

Another study also showed significant benefit in complete response rate to therapy and prevention of myelosuppression and secondary infections when thymus peptides were added to the regimen (10,11).

Therefore, in the ***Cologne Model***, thymus peptides are used:

1) To enhance bone marrow function and protect the patient against myelo-suppression of standard chemotherapy;
2) To support bone marrow recovery after radiation and chemotherapy;
3) To prevent secondary infections due to immunosuppression caused by standard chemotherapy and surgical interventions;
4) To increase complete and partial response rate to anticancer therapies;
5) To improve lymphocyte function and biological defence mechanisms.

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6 PROCAINE – BICARBONATE INFUSIONS

6.1. Introduction

The pH of blood is kept stable within extreme narrow margins by a very intricate basal function of the organism. Through millions of years of evolution, this basal function has been significantly developed in mammals, and is considered to be one of the most advanced physiological functions in man. The use of energy (oxidative processes) is always accompanied by the production of acids, through which the pH will be lowered. The intricate basal function is brought about by the interaction of kidneys, lungs, gut and skin, which will usually excrete the surplus of acidity. But, in cases of chronic disease, each biological system can be exhausted, including the acid-base equilibrium. In case of chronic viral infections and cancer, a depletion of the bicarbonate buffer can add to the catabolism and fatigue of the chronically ill. Thus, becoming a major risk factor for morbidity and mortality.

6.2. Acid-Base equilibrium in cancer patients

(Chronic) Inflammatory processes and metabolic processes in cancerous cells are associated with the generation of free oxygen radicals (FOR). Rusu *et al*. found that procaine (and its metabolite diethylaminoethanol DEAE) inhibits the generation and release of super oxide anion in a non-enzymatic system (1), and Andreadous *et al*. found that a series of ethanol amine derivates inhibit the generation of super oxide anion radicals in a xantine-xantine oxidase system, the respective products also having a significant anti-inflammatory action (2).

In normal physiological processes, FOR are released by the respiratory burst of polymorphonuclear cells (PMN), like neutrophils, macrophages and monocytes. In chronic disease, as a result of an elevated production of FOR and / or a depletion of antioxidants, FOR can induce severe alterations of cell macromolecules, expressed by lipid peroxidation, which leads to destruction of cells. It is strongly suggested by the work of Dolganiuc *et al*., that procaine and DEAE inhibit significantly the release of free radicals by PMN during a respiratory burst (3).

Tumour cells have a less sufficient metabolism and produce mainly lactate instead of carbodioxide and water. One could say, that tumour cells do not "breathe" but "ferment". The normal metabolism of glucose is aerobic and one molecule of glucose provides 38 molecules of ATP (energy). Under anaerobic circumstances however, one molecule of glucose will provide only 2 molecules of ATP, and instead of CO2 and H2O, lactate is being produced. Lactate can accumulate locally and cause pain and discomfort, like in *intermittent claudicatio*, or systemically, and cause elevated plasma levels. Loss of appetite (*anorexia*) and wasting (*cachexia*) in cancer and in other chronic diseases, like HIV infection, can be explained, in part, by the increased need for glucose and the elevated production of lactate.

Thus, in summary, one could say, that tumour cells have an increased need for glucose to cover their energy requirements, which are 20 times higher than of normal cells. As a consequence, an increased use of glucose and a depletion of glycogen storage in the liver take place, and an abundance of lactate is consequently being produced. On the long run, the increased lactate production will deplete the bicarbonate buffer in the blood, bring about pain and discomfort and will initiate catabolism, which will lead to *anorexia* and *cachexia*.

In the ***Cologne Model***, cancer patients, and patients with other (chronic) conditions, requiring support to overcome the burden of the negative effects of increased lactate production, will receive infusions with 400 ml NaCl (0,9%) with 120 ml NaHCO3 (8,4%), and 5 ml of Procaine 2% added.

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7 ORTHOMOLECULAR THERAPY

7.1. Introduction

Fundamentally, orthomolecular therapy is a supplementation of essential vitamins, trace elements, minerals, amino acids and polyunsaturated fatty acids. Often, in cancer patients, because of life style, their underlying disease, or because of the effects of chemotherapy and radiation, there is a depletion or unbalance of many of these elements.

It is estimated that 60% of all cancer patients have an unbalanced diet and are lacking essential vitamins, trace elements, and alike (1-3).

Usually, in healthy individuals with a balanced diet, a short course of a conventional medicine will not have a negative effect on the nutritional status. However, in the case of a long-term application of a conventional medication or in polypharmacotherapy, there can be an interaction with absorption of nutrients from the gut and/or the metabolism of these substances. Xenobiotica as an example, can alter the metabolism of essential nutrients through affecting the Cytochrome P450 system in the liver, inhibit or accelerate the excretion, inhibit absorption by changing the pH in the gastrointestinal tract, or change the intestinal flora, etc.

7.2. Therapeutic interventions

From birth on, the development of the gastrointestinal tract and the immune system (GALT) depends, to a large extent, on the intake of nutrition and the colonisation with appropriate intestinal flora (see chapter 8: Improvement of intestinal mucosa and flora).

A “healthy diet” is universally recognized as the main prophylaxis of tumour growth and inhibition of metastatic disease. But what is a healthy diet? A regular diet in industrialized countries usually contains more than enough calories, protein and fats. But, after more than a century of monoculture and the use of artificial fertilizers and pesticides, common food stuffs are usually loaded with pesticides and antifungal agents and depleted from most trace elements, like zinc, selen, cobalt, essential amino acids, and vitamins.

In addition, many products are refined and thus, loose part of their nutritional value. Even in a mixed and varied diet, easily, a deficiency of trace elements and other nutrients can develop over time.

Therefore, in the ***Cologne Model***, a screening of the blood for main trace elements, antioxidants and vitamins is conducted. If deficiencies are found, supplementation will be recommended.

Phytoestrogens, phenoles and flavonoids inhibit growth of (pre-) cancerous cells (4,5). Therefore, in the ***Cologne Model***, patients will be advised how to guarantee a sufficient intake of all these nutrients. Supplementation of phytoestrogens, flavonoids and phenols are usually suggested.

Since the initiation of tumour growth is correlated with an increased burden of endogenous and exogenous oxygen radicals (6), supportive therapeutic interventions with strong antioxidants, like the combination of vitamin C and E, beta-carotene and marine fatty acids, are part of the ***Cologne Model***.

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8. IMPROVEMENT OF INTESTINAL MUCOSA AND FLORA

8.1. Introduction

The gastrointestinal tract and its symbiosis with micro-organisms has been an issue amongst physicians and researchers alike. Usually, intestinal micro-organisms (bacteria and fungi) have been considered to be detrimental to the human host. Recently, research has shown, that the flora plays an important role in the vitality of the human host.

In the body, the intestinal mucosa forms the largest contact surface with the outer world (skin 2 M2; lung 100 M2; gut 500 M2). The intestinal tract forms an open functional system with about 300 - 500 M2 active resorption surface for nutrients, water, bile salts and secretions by glands within the gut for protection against micro-organisms and dangerous antigens and toxic material. Also, the gut excretes IgA and waste products into its lumen.

8.2. Microbiology of the gut

In total, it is estimated that in an average adult, there are about 1000 trillion (10 hoch 15) bacteria living in the gut, mainly in the colon. This is 100 times more than the total amount of cells in the adult human body. The gut flora contributes about 700 grams to the total body weight. At birth, the gut is sterile. The colonisation of the gut is an ongoing process and can be divided into four stages (1):

1) Phase I: initial colonisation through ingestion of bacteria from the mother during the birth process of mainly aerobic bacteria (*E. coli*, *Enterococcus*, etc.);
2) Phase II: establishment of the early flora from the second week post partum on. Now, the gut is colonised by micro-organisms which break down complex carbohydrates, and aerobic and anaerobic bacteria (*Lactobacilli*, *Bifidobacteria*). The newborn will ingest and be colonised mainly by bacteria from the mother though direct contact with the skin and through breastfeeding;
3) Phase III: colonisation through micro-organisms from food stuffs other than milk. Usually, these bacteria are anaerobe (*Eubacterium*, *Veillonella*, *Fusobacterium*, *Megasphaera*, *Clostridium*, etc.). At this stage, the adult situation is achieved. There is being established a kind of equilibrium between many of the various micro-organisms;
4) Phase IV: stage of the elderly. In the elderly, there is a shift in the equilibrium between the aerobic and the anaerobic bacteria with an increase of the Clostridium species and a decline of the Bifidobacteria.

The oxygen use of the aerobic bacteria is so high within the gut that anaerobic bacteria live in symbiosis with aerobic bacteria and further break down of what is left of the foodstuffs.

8.3. Importance of the intestinal flora for the human host

The development of the gastrointestinal tract and the immune system is highly influenced by the intestinal flora (2-3). Therefore, in cancer, allergies, chronic viral diseases, and other diseases, which are rooted in a malfunctioning of the immune system (immune deficiencies), the content and quality of the intestinal flora are of utmost importance.

Also, the absorption of many vitamins is dependent of the intestinal flora, like Vitamin K, and several of the Vitamin B group (B1, B2, B6, B12), folic acid, biotin, niacin, pantothen acid (4).

8.4. Importance of the intestinal flora for the development and functioning of the Gut Associated Lymphoid Tissue (GALT)

With food intake, many potentially infectious microorganisms and detrimental toxins (antigens) enter the gastrointestinal tract. In the submucosal layers of the gut, well-developed lymphoid tissue (the Gut Associated Lymphoid Tissue or **GALT**) is present to prevent invasion of abnormal microorganisms and toxins. In no other organ system, the immune system is so well developed and omnipresent as in the gastrointestinal tract. The plaques of Peyer are a good example of GALT. Within the lymphocyte population, especially T-lymphocytes in the mucosa and the *lamina propria*, play an important role in preventing a systemic immune reaction to food antigens (oral tolerance). In case of food allergies, but also the initiation of allergies over the mucosa, like in hay fever and contact allergies, there is a dysfunction or deficiency of GALT. Therefore, in case of allergies, other than triggered by intake of certain foodstuffs, the intestinal flora should be examined as well.

Under physiological conditions, plasma cells in GALT synthesise and excrete IgA into the lumen of the gut. In contrast to all other classes of immunoglobulins, IgA is resistant to many endogenous and bacterial proteases, and cannot be broken down after it has been excreted into the lumen. IgA works like “antibody painting” and protects the mucosa from invasion of detrimental microorganisms and toxins. In other words, IgA is the “first line of defence” (5).

Diet has a definite influence on the functioning of GALT. (see Chapter 7: Orthomolecular Therapy). Therefore, in the ***Cologne Model***, attention is given to diet and intake of trace elements, vitamins and cancer-protective plant substances, like phenols, flavonoids, etc.

A proper development of the immune system in the gut and a balanced intestinal flora will add to health, and its maintenance. In case of (chronic) disease, particular attention must be paid to the composition of the various bacterial subpopulations within the gut.

In the Cologne Model, prevention medicine also plays an important role. Therefore, attention is paid to the composition of the intestinal flora as well, as, over time, a misbalanced flora can add to the risk of developing cancer, allergies and chronic disease.

8.5. Therapeutic strategies and interventions

There are three main considerations regarding therapeutic interventions:

1) “Is the current illness directly connected with the barrier function of the gut?”
2) “Does the current illness have a direct effect on the intestinal flora?”
3) “Can the course of the current illness positively be influenced through affecting the intestinal flora?”

8.5.1. Change of the milieu

Micro-organisms have a tremendous flexibility in the physiology of their metabolism, compared to plants and animals. In part, this is due to their tiny dimensions. On average, a bacterium contains less than 100.000 protein molecules. If, at a given time, certain enzymes are not needed, they are just not produced. Micro-organisms have a tremendous metabolic (anabolic) potential. A cow of 500 kg produces per day approximately 1 kg protein. Under perfect circumstances, 500 kg of micro-organisms could produce more than 10.000 kg of protein in the same time.

The pH of the intestinal milieu plays an important role in the metabolism and reproduction potentials of micro-organisms. The optimal pH of the gut (colon) is <7.0. Usually, in chronic disease and cancer, the pH is clearly >7.0. Therefore, in these cases, the pH of the milieu must be lowered. This can be brought about by dietary changes, like increasing the intake of fibre and lactulose, and of *Lactobacilli*, and decreasing the intake of proteins.

Fibre and lactulose are usually plant derived and consist of a mixture of cell membranes and cellulose, which cannot further be broken down by the human digestion processes. A fibre-rich diet lowers blood cholesterol and stimulates peristalsis. Through increasing gut motility, passage of food rests (*faeces*) is hastened and thus, toxic substances, among them bile salts, free ammoniac, psychopharmaca and antibiotics, have less contact with the intestinal mucosa. Thus, in this way, it can be understood that fibre rich nutrition lowers the risk of colon cancer (6).

8.5.2. Reduction of protein intake
Some of the dietary proteins reach the colon. Here, bacteria, which can break down proteins, are available. Among them are various *E. coli* and *Klebsiella* and *Proteus* species. Through proteolysis, free ammonia and amines are formed, which make the milieu of the gut more alkaline (ph>7.0). Therefore, dietary intake of proteins should be modest. Usually, a vegetarian diet is rich in fibre and relatively low in protein.

8.5.3. Value of Lactobacilli supplementation
Bacteria like *Bifidobacilli* and *Lactobacilli* lower the pH of the colon and can be an adjunct therapy in the treatment of cancer patients and patients, who received prolonged antimicrobal therapies.

8.5.4. Immunomodulation through microbiological interventions
Fundamentally, any immunomodulation through therapeutic intervention only makes sense in diseases, where the cause of the disease lays within the immune system itself, or where through medical interventions (antimicrobal therapies), the intestinal flora has been severely altered. One parameter is the IgA concentration in the stool (6).

Through application of commercially available microbiological preparations, the milieu of the intestinal lumen can be influenced positively, and thus, an effect on GALT can be achieved.

In this context, *Saccharomyces boulardii* plays a special role in immunomodulation and improvement of the milieu of the intestinal lumen (7,8). *Saccharomyces boulardii* can be given prophylactically in case of antimicrobal therapy to prevent diarrhoea, etc., or to treat imbalances of the flora after such a therapy (9).

8.6. Pancreas insufficiency

In chronic disease, the exocrine function of the pancreas can become insufficient. Often, this condition is late or never diagnosed. If an insufficiency of the exocrine function of the pancreas is suspected, in the ***Cologne Model***, cancer patients are tested for their pancreas function and substitution of pancreatic enzymes is initiated when an insufficiency has been documented.

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9. WOMEN’S HEALTH

9.1 Menopausal Symptomatology

Menopausal women frequently request more natural approaches than hormonal substitution for menopausal symptoms. Many women express concern about possible teratogenic effects of long-term hormonal substitution therapies.

The working of Isoflavones (phytoestrogens) has been studied extensively in the treatment of menopausal symptoms in women. Isoflavones show a structural resemblance with normal estrogens(1). They bind selectively to estrogen receptors (2). Especially cardiovascular symptoms and osteoporosis are positively influenced (3,4).

Interestingly, in countries with phytoestrogen-rich diets, like in many Asian countries, several forms of cancer are less common than in our western world (5).

Also, the intake of Isoflavones improves elevated blood cholesterol and lipid levels (6).

Therefore, in the Cologne Model, menopausal women and women post ovarioectomy, will receive isoflavones in therapeutic doses (usually, an standardized extract of clover and soy isoflavones will be administered).

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