The Biological Approach to Breast Cancer

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Dear members of the congress, ladies and gentlemen:

I am grateful to Mr. Abel for kindly inviting me to this major congress of alternative medicine and naturopathy. I have been involved in the art and science of healing for over 35 years and I have reflected deeply on how cancer develops and, specifically, how breast cancer should be treated.

It is obvious that the usual approaches to breast cancer are often failing most of the time and, faced with a disaster, I believe there is a greater need than ever to link different medical points of view and diverse treatments. Over the past century, oncologists have paid more attention to the role that genetic mutations play in promoting abnormal growths that become malignant and have constructed a historical treatment option based on tumor destruction with surgery, chemotherapy and radiation.

Although virtually all modern therapies of cancer are directed at tumor cells, laboratory evidence indicates that it may also be fruitful to treat the endothelial tissue environment as well.

Growing evidence shows that a tumor can grow only to about 2 mm and will then stop unless there are growth factors available from matrix storage and immune cells that help to induce tumor blood vessels.
How cancer arises

To begin with, we know from basic research that DNA mutation is a necessary first step for a normal cell to enter a malignant process involving oncogene activation and immunosuppression as genetic alterations accumulate in an initiated clone.

But at variance with the genetic standpoint, our point of view, endorsed by other progressive doctors and renowned researchers, may explain the various causal factors inside the tissues that influence a cell to become cancerous, why breast cancer progresses in an unhealthy environment and why breast cancer cells grown in a culture of normal breast extracellular matrix behave like normal cells.

A crucial experiment conducted by a team of researchers from the University of California, Berkeley, discovered that the healthy influence of normal breast extracellular matrix causes cancer cells to behave normally even though they were genetically altered. Yet when the same cells were put into an artificial environment they again behaved like cancer cells. This shows that cancer cells are not isolated and that the general state of the body influences their capacity to thrive.

We understand that cells make certain proteins, growth factors, cytokines and enzymes that are messengers telling surrounding cells what to do. We call it “interaction” and it is probably a determinant of cancer cell growth. In vitro studies have demonstrated that the aberrant differentiation of breast tumor cells can be restored at least partially to normal differentiation by interactions between adjacent normal cells and the extracellular matrix (ECM). (Figure 1a)
Connective tissue may initiate cancer

Connective tissue, which supports the epithelium, is rich in blood vessels, infiltrating lymphocytes, fixed macrophages and mast cells. It is primarily composed of macromolecules embedded in an extracellular matrix that provides a conduit for the transfer of electrolytes, trace elements, vitamins, hormones, enzymes, growth factors, proteins, etc… to and from the cell surface.

The structure of interlinked fibers and gel-like matrix consists of enormous proteoglycans, which play a key role in chemical signalling from one cell to another, together with polysaccharides and 13 different types of collagen.

Matrix composition plays an active role in modulating cell behaviour and certainly plays a major role in the regulation of angiogenesis. Levels of angiogenesis promoters or inhibitors may be balanced or unbalanced in physiological and pathological processes depending on stimulatory factors.

Link between connective tissue and epithelial cells

Connective tissue provides a barrier to tumor invasion but also plays an essential role for epithelial cells.

There is no direct link between epithelial cells and blood vessels, lymph vessels or nerves because of the connective tissue (matrix).

All the nutrients, oxygen, nerve supply, and hormonal stimuli required by the epithelial cells have to pass through the matrix to reach their targets.
Thus, malfunction of the connective tissue leads to a nutritional deficiency, a decreasing oxygen supply to epithelial cells and autointoxication of cells through the accumulation of wastes produced by residual toxins. Macromolecules from undigested food increase oxidative potential and hyperacidity which can modify and change the matrix and activate mitotic factors.

One example is protein growth factors found in extracellular matrix storage to stimulate or inhibit antiangiogenic factors.

Other examples of angiogenesis regulatory mechanisms are macrophages, T-lymphocytes and mast cells during inflammatory reactions, since they may contribute to the angiogenic switch in breast cancer. Macrophages can influence the composition and structure of the extracellular matrix through the production of proteases, which in turn influence endothelial cells and new capillary growth (1-2). Macrophages respond to angiogenic signals from cancer cells to induce pro-angiogenic and MMP1-MMP2.

**Water structure influence on information transfer**

It is known that the body consists of 70% of water, which plays a crucial role in our survival. The molecular structure of water greatly influences information transfer to the organism and assists in the absorption of nutrients by cells.

**Influence on the structure of connective tissue**

In addition to the structure of water the anatomical structure of the connective tissue, consisting of proteoglycans and glucosamines, is sensitive to ROS activity, and may be damaged by massive oxidative stress and local hyperacidity with changes in the structure and fluidity of the connective tissue.
In the case of chronic toxicity, inflammation and high oxidative potential the fluid consistency of the matrix becomes stiffer, causing the connective tissue to become more gelatinous, and thereby modifying the metabolic structure of the connective tissue and epithelial cells.

**Chronic inflammation and edema**

We hypothesize that autointoxication and acute or chronic inflammatory processes arising from a reduction in antioxidant defences may cause edema in the connective tissue through specific prostaglandins and leukotrienes metabolised from arachidonic acid, with a strongly negative effect on epithelial cells including factors stimulating mitotic activity.

**Arachidonic cascade**

The metabolism of arachidonic acid, which is increased by an excess of dietary meat and dairy consumption, plays a key role in highly inflammatory processes, which are localised in the soft connective tissue matrix.

The enzymatic generation of prostaglandins and leukotrienes from arachidonic acid via the cyclooxygenase and lipoxygenase pathways also promotes free radicals, which have long been implicated in inflammatory processes and edema.

The generation of reactive oxygen species (ROS) may damage the cell membrane, including membrane polyunsaturated fatty acids, which
perturbs the synthesis of prostaglandins, decreasing PGE1 and increasing PGE2 to excess, thereby promoting chronic inflammation.

**Harmless effects of prostaglandin PGE2 on edema**

An excess of PGE2 is highly inflammatory in several ways.

- By increasing vascular permeability and promoting local edema.
- By acting synergistically with histamine and leukotrienes to intensify inflammatory edema.

During the inflammatory process, mast cells (CTMS) release histamine and heparin, increasing the inflammatory pathway to cause further edema and promote angiogenesis.

PGE2 also has a potent immunosuppressive effect, with down-regulation of T-cells, B-cell proliferation and the cytotoxic activity of NK cells (3), while inducing the activation of metalloproteinases MMP2 and MMP9, a critical step for angiogenesis and the degradation of the extracellular matrix which is an independent prognostic indicator of primary breast carcinoma.

Oxidative stress through high free radical activity and antioxidant deficiency causes amplified cytokine expression and excessive levels of excitatory cytokines cause subsequent damage to healthy tissue including acute and chronic inflammation (4).
Cyclooxygenase 2 (COX2) involved in tumor development and progression

The cyclooxygenase enzymes that catalyse conversion of arachidonic acid to prostaglandins and thromboxanes may also be involved in tumor development progression and invasiveness.

Several studies have shown a relationship between angiogenesis and COX2 expression.

Overexpression of COX2 induces the pro-angiogenic factor Vascular Endothelial Growth Factor (VEGF) which is the most potent angiogenic protein, as well as interleukines IL-6 and IL-8 (5-6), and may be activated by nitric oxide, superoxide anion or through the production of peroxynitrite and hydroxyl radicals.

Another example is the overexpression of COX2 associated with the activation of metalloproteinases (MMP1 – MMP2), which therefore play a key role in angiogenesis and tumor expansion in breast cancer, since COX2 expression is also increased by 40-60% in breast cancer with excessive ROS activity and overexpression of superoxide dismutase. Other examples associate overexpression of COX2 with the progression of estrogen–dependent breast cancer by autocrine and paracrine mechanisms or by indirect upregulation of aromatase activity.

PGE2 also stimulates aromatase transcription leading to increased levels of oestrogens, thereby involving coexpression of the cytochrome P450 enzyme aromatase and COX2 in human breast cancer.

COX2 is elevated in many tumors and may downregulate apoptosis, a crucial keep in tumor promotion, and upregulate proliferation.
Today more attention is being paid to COX2, since a significant relationship between overexpression of COX2 and survival breast and lung cancer has been reported in a retrospective study (9). Thus, inhibition of COX2 leads to a subsequent reduction in levels of PGE2 and its analogues acting as tumor promoters.

**Consequences of edema**

Edema of the connective tissue resulting from an inflammatory condition interferes with nearly all the exchange processes involved with nutrients, oxygen transport and detoxification of epithelial cells.

The consequence is an increasing waste accumulation, intracellular hypoxia in the epithelial cells and tumor expansion.

When deprived of oxygen the tumor cells respond to external stimuli. The most potent external stimulus of angiogenic factor expression is hypoxia.

Hypoxia typically increases angiogenic factors such as Vascular Endothelial Growth Factor (VEGF) (10-11) by inducing a signal cascade pathway. It also stimulates fibroblasts to produce more collagen, which also facilitates angiogenesis, since collagen synthesis is needed for the basement membranes of new blood vessels.

For a new blood vessel to be formed, endothelial cells must respond to biochemical signals and begin to migrate towards one another to form microtubes that eventually become new blood vessels.
The next step in the angiogenesis signal cascade is the increased proteolytic activity of matrix metalloproteinases such as interstitial collagenase (MMP1) and gelatinase (MMP2), which are necessary for the degradation of the ECM to provide a microenvironment in which activated vascular cells can proliferate, invade and migrate away from the preexisting parental vessel and form new blood vessels.

However \textit{in vitro} studies have found that antioxidants can successfully inhibit VEGF production, which is included prominently in my comprehensive basic approach.

\textbf{Anaerobic respiration}

Chronic hypoxia may profoundly affect epithelial cells in several ways.

First, it impairs the detoxification process since increasing oxygen supply is required to detoxify cellular waste products and decrease the amount of CO2 produced.

In epithelial cells dying as a result of starvation and autointoxication, ROS activity increases while oxygen deficiency in mitochondria is responsible for an excess of unordered electrons acting as free radicals, caused by overproduction of electrons in the respiratory chain which cannot couple to oxygen due to the decreasing amount of oxygen available.

Warburg’s original hypothesis stated that cancer originates from irreversible injury to respiration, but that cancer clones can function anaerobically while retaining highly competitive growth characteristics.
Thus, the cells switch over from phosphorylation to anaerobic glycosylation for ATP energy production, with increasing free radical activity and decreasing antioxidant defences, which may lead to cellular hypermutability.

Thus the output of
ATP energy decreases considerably from
38 molecules ATP to
2 molecules ATP

This energy output is a major cause of tumor development since ATP regulation is necessary for DNA repair and immune function. It controls all the constituents needed for the synthesis of genetic material such as RNA and DNA. Indeed, tumor cells frequently have defects in their DNA repair program and apoptosis.

High levels of ATP are needed to maintain a high degree of differentiation in tissues and to control certain genes. Because of decreasing energy supply, tumor cells become less differentiated than healthy cells.

Energy is also possibly needed for the regular replacement of apoptotic cells by stem cells, which are located close to the basement membrane and have to differentiate into organ-specific cells.

High levels of free radical activity, which produces structural damage, inhibit the physiological propagation of the replacement control information, which may lead to a disordered replacement of apoptotic cells and increase the risk of mitotic activity.

Thus, connective tissue edema leads to alterations in the metabolism of epithelial cells through a stepwise accumulation of genetic events until the advanced state of metastatic disease is reached.
Tumor invades the body

After multistep factors involving mutations, initiation, promotion and progression, leading to the metastatic condition which in breast cancer requires about nine years, the tumor induces growth of its own blood vessels and, by loss of adhesion breaks up the basal lamina and invades the underlying connective tissue. It causes matrix degradation by increasing the expression of selected proteolytic enzymes, including matrix metalloproteinases (MMP – MMP2) or plasmin, which can degrade fibrin, and components of the extracellular matrix. Cells then enter the circulation by penetrating nearby fragmented and leaky blood vessels or (in the case of breast cancer) preferentially lymphatic vessels.

The tumor cells interact with blood components and must survive in the circulation, arrest in the microvasculature of the target organ (chiefly in lung, liver and bones), exit from this vasculature and may grow after a dormancy period in the target organ by inducing angiogenesis.

Surgery and metastasis risk in breast cancer

In breast cancer removal of the tumor by mastectomy is not decisive since surgery may increase the metastatic risk to 70% and increase death from breast cancer in younger women (Lancet 2000).

Five year survival with cancer that has spread beyond the primary site region is about 20%.
Removing a large tumor or mastectomy is not a 100% guarantee of cancer cell elimination, since 0.1% of tumor tissue (1 mm$^3$) and $10^6$ cells usually remain.

Removing the whole tumor means also removing the nonangiogenic cells, since some of the metastases contain cells that are already angiogenic and thus grow rapidly. Other metastases contain mainly nonangiogenic cells and may lie dormant for several years before being stimulated by a change in environment.

If 0.1% of tumor cells remain without anti-angiogenic factors, they will start to grow on stimulation by angiogenic factors as shown in many cases, even in breast implants.

In the case of surgical tumor removal, secondary tumor near the first site region or chest area can grow faster since cancer cells are already mutated. New tumors can developed after 6-12 months and are subject to further chemotherapy or radiation. Cytotoxic treatment leads in most cases to a clonal selection of tumor cells, making the disease more resistant and less curable.

This is why antiangiogenic therapy in breast cancer is important before surgery and after removal of the tumor, in order to inhibit the development of new blood vessels and tumor growth (12).
A comprehensive basic approach

The main goal is to detoxify and improve the quality of the extracellular matrix by regulation of the basic ground substance. By elimination of chronic accumulation of endo- and exotoxins, the load from massive oxidative stress can be reduced and the level of angiogenic factors between inhibitors and promoters become balanced.

Suggested Therapies:

A – Enzyme Yeast Cells

Enzyme yeast cell preparations in my hands contain all the necessary vital and biological substances, such as vitamins, minerals, hormones, enzymes, coenzymes, glutathione and cysteine to detoxify and stimulate ATP production. Enzyme yeast cells regulate the basic ground substance to maintain the quality of the ECM. (13)

Suggested doses: 20 ml – 3 times per day.

B – Fresh Bamboo Leaf Extract

Many years ago I discovered the medicinal and detoxifying properties of fresh bamboo leaf extract, which is rich in many enzymes, natural polysaccharides and amino acids, and acts as an SOD-like activity. One important property of fresh bamboo leaf extract is the small size of water molecules in the extract, which is effective for better information transfer and absorption of vitamins and minerals.
Fresh bamboo leaf extract also increases the redox potential and energy level of patients, as confirmed by electromagnetic measurements and chemoluminescence. During my practice with breast cancer patients, I observed significant improvement in physical condition, greater strength and reduction of metastasis in target organs.

My fresh bamboo leaf extracts come from a variety of small size bamboo growing at very high altitude in the mountains of Asia. 100kg of fresh leaf is necessary to obtain one litre of pure water to extract only 10cc of concentrated active substances. It has been shown it contains a very high concentration of these active substances, including very sensitive enzymes.

Suggested doses: 40 ml – 3 times per day

**C - Therapeutic modification of the arachidonate pathways**

Therapeutic modification of the arachidonic acid pathway and elimination of chronic inflammatory processes is necessary to reduce the level of tumor-promoting prostaglandins and leukotrienes. Reduction of meat intake is strongly recommended, since it is rich in arachidonic acid which can build up an excessive pool (in Western diets 200-1000 mg daily, which is up to 200% the maximum amount required by the body).

**Suggested supplements:**

Omega 3 - fatty acids, especially EPA (eicosopentaenoic acid) and DHA (docosahexaenoic acid) in equal quantities (1g of each daily), Vitamin E (1g per day), squalene (3g per day) with the low molecular antioxidant compound Anoxe (about 18g per day), are some of the suggested
supplements from our clinical practice that reduce or eliminate ROS activity and chronic inflammation.

Inhibition of cellular proliferation

Antioxidants in general and the enzyme superoxide dismutase (SOD) inhibit malignant transformation (14). The low molecular weight antioxidant compound Anoxe, which has SOD-like activity, creates a reductive potential in the tissue and decreases inflammation. Based on various lines of experience, it may inhibit tumor growth, differentiate cancer cells and induce apoptosis (15) to assure a successful prevention of recurrence of metastases.

We know that SOD is one important enzyme used as a bioorganic antioxidant in diseases with excessive chronic inflammation and linked to breast cancer, but most of the oral administration of SOD and catalase is ineffective since the enzymes are poorly absorbed and rapidly degraded in the gastro-intestinal tract. In contrast, Anoxe is rapidly absorbed by the body with strong free radical quenching activity (16). As we have realized, high ROS activity may damage healthy tissue, activate chronic inflammation and potentially activate PGE2 and COX2. Therefore low molecular weight antioxidant can reduce or neutralize excessive ROS activity that initiates the inflammatory cascade and play a key role by creating a shield of protection during cytotoxic anti-cancer therapy. During the past decade, a wide range of investigations and clinical experiences have shown that SOD and antioxidants are some of the best answers in cancer treatment, while from recent publications in various countries SOD seems to be attracting more interest from the medical research community as a potential anti-cancer drug.
**Nucleic acids (exogenous nucleotides)**

Nucleic acids/nucleotides from DNA and RNA are an important functional food that activates all the processes of cell repair, promotes differentiation, induces apoptosis and inhibits proliferation of cancer cells. (Morishige F. et al - 1985) enhance NK cells and protect the nucleus against ROS damage.

A Japanese team has shown that nucleic acids exhibit antioxidative effects on the oxidation of linoleico acid by air (Matsuhita et al 1983) and remove low molecular products of nucleic acid degradation (ATGC) resulting from oxidized DNA. They have also demonstrated that the antioxidant activities of DNA are more powerful than additives such as vitamin C and E, which are in fact poorly active against lipid peroxidation.

In a healthy body, damaged cells that cannot be repaired by DNA enzymes are directed into the p53 apoptosis pathway in order to commit suicide. Therefore the p53 route is our first guardian against cancer and depends on exogenous nucleic acids supply.

A number of researchers have show that exogenous nucleotides have the ability to reverse the damage to normal cells caused by anticancer drugs but without promoting the proliferation of cancer cells. Exogenous nucleic acids are a vital food supplement which revitalizes the cells and helps DNA synthesis to maintain all biological functions.

The Nucleosan formula developed by Serge Jurasunas contains the 4 types of nucleotide (AGCT) at the same concentration for fully activity. It protects tissues and bone marrow from damage by cytotoxic anti-cancer drugs, enhances chemotherapy and increases physical and brain vitality.
Suggested doses – (300 mg capsules) – 3 g per day

**Squalene**

Squalene is an isoprenoid obtainable from shark liver oil but also found in the human body. In Europe the property of squalene as an agent for disease prevention or treatment, especially cancer, is still relatively unknown. However since 1983 squalene has been included in most of my cancer protocols and particularly for breast cancer.

Among several properties, squalene has demonstrated its ability to interfere with the activation of the RAS oncogene implicated in breast cancer (17) and to act directly against tumor activity. Mutations of RAS lead to uncontrolled activation of cell division and therefore play an important part in transformation.

The enzyme ornithine decarboxylase (ODC) is also linked to breast cancer, showing the highest differential expression of essential growth proteins (18). ODC is the key regulator in the synthesis of polyamines, which are essential for cell proliferation. However, ODC becomes activated during cell transformation induced by carcinogens increasing the concentration of polyamines in tumor cells and can also be found in large quantities in the blood and urine of cancer patients.

Some researchers have demonstrated that, on the contrary, tumor growth and the formation of metastases decrease when polyamine synthesis is blocked.

One interesting discovery is that squalene may inhibit induction and reduce tumor formation (19).
In breast cancer, treatment with squalene protects tissues from acute or oxidative stress, especially from radiation exposure that leads to massive release of excitatory cytokines, resulting in severe inflammation.

**Anti-angiogenic Therapy**

Angiogenic therapy is also a major goal, designed to starve the tumor of oxygen and nutrients by neutralizing new blood vessels and thereby shrinking the tumor.

Significant results have been obtained with liquid cartilage extract (LCE) that contains molecules (glycosaminoglycans) that can stop the proteolytic activity of metalloproteinases (MMPS).

Anti-metalloproteinase
Anti-inflammatory

Shark cartilage demonstrates anticancer and antitumor activity and inhibits collagenase *in vivo* (Boik 1997).

The application of LCE (Car-T-Cell) is a part of our breast cancer management as follows:

1 – In the case of breast cancer, taken if possible before surgery.
2 – For large tumors with major inflammation or inoperable tumors.
3 – After surgery to enhance chemotherapy and thereafter to prevent tumor recurrence.

Additionally, Genistein (18) and green tea inhibit angiogenesis and we encourage patients to take both as supplements during treatment.
Other approaches include nutritional support, which plays a decisive role in the treatment of breast cancer.

Vitamins A, C, E, beta-carotene, selenium and linoleic acid deficiency are associated with the disease of breast cancer and suggest supplementation.

In my experience daily intake of Sun Chlorella seems to be the best nutritional support for breast cancer patients. It contains more than 20 different vitamins, minerals, amino acids, nucleic acids and enzymes, plus glutathione. Sun Chlorella is also very rich in chlorophyll and beta-carotene. Sun Chlorella showed significant effects on cellular immunity and increased immune resistance against external agents or cytotoxic therapy.

Raw organic vegetable juices are highly recommended and can be mixed with different supplements to make cocktails that may have stimulating effects and anticancer properties (consult my internet page – Breast cancer theories and therapies).

Psychological intervention is often necessary since, breast cancer is an emotional disease linked with anxiety, depression and high oxidative stress, which usually increase after the surgery and during chemotherapy.

Many researchers have demonstrated that breast cancer/stress can affect the immune system in several ways, but usually by reducing the ability of individuals with cancer to resist disease progression and metastatic spread and by lowering the levels of NK and T lymphocytes (21). Other recent work by German researchers demonstrated that cancer cells are attracted by
neurotransmitters such as dopamine which are released during anxiety in breast cancer and encourage metastatic spread through the matrix.

My booklet “An Integrative and Naturopathic Approach to Breast Cancer” (translated into German) offers various suggestions for psychological intervention.

**Conclusion**

Our belief that all cancer cells must be killed may not be entirely correct. On the contrary, there is reason to believe that cancer cells can be controlled through different mechanisms, such as differentiation, apoptosis, immune surveillance, detoxification, etc…

Metastasis occurs usually when the cancer has been treated and leads to invasion of other organs of the body. We all know that standard therapies are limited and, even if beneficial in the beginning, become toxic and over the years fatal to patients.

Sometimes local recurrence is very fast and depressing for the patients.

On many occasions I have demonstrated that breast cancer is not a tragedy and under naturopathic treatment, selected complementary therapy, a psychological approach and good experience that includes the disease and the individual, patients can return to their former healthy condition.

Thank you for your attention.
For more details, publications and the complete treatment of breast cancer consult my Internet homepage.

- Breast cancer theory and therapies.

- A naturopathic approach to breast cancer with complete therapy. (In German)

- Therapeutic application of a new low-molecular weight antioxidant compound (Anoxe) in ROS activity. (In German)

- The Biological Approach to Breast Cancer (including new developments in treatment).

- Far-Infrared Ray Emitting Stone (SGES) to treat Cancer and Degenerative Disease.

- My new research program “Complementary Therapies in Oncology”

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