



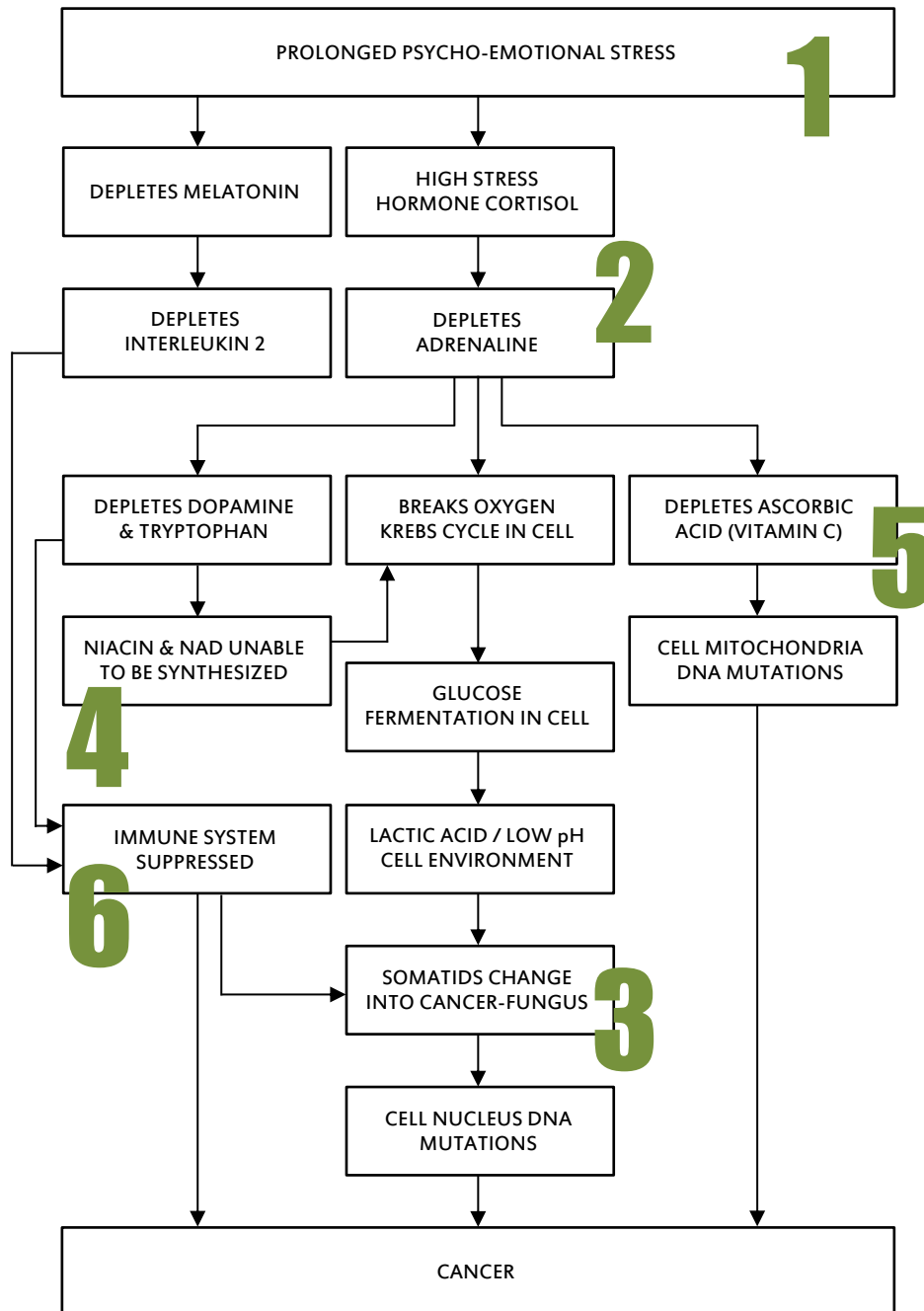
**PSYCHO-ONCOLOGY:  
THE 6 PHASES OF CANCER**

# Psycho-Oncology: The 6 Phases of Cancer



An Evidence-Based Thesis Revealing the Causal Relationship between Stress and Cancer

## Flow Chart



*Psycho-Oncology: The 6 Phases of Cancer*

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An Evidence-Based Thesis Revealing the Causal Relationship between Stress and Cancer

## Introduction

Cancer has long been associated with stress; however within mainstream oncology stress is generally considered of relative low importance as the primary causal factor in the genesis of cancer. Inspired by God, spiritual messenger Glen Russell brings forth new never-before-seen concepts identifying stress as the primary instigator of cancer. This document has been created to help medical staff, researchers and lay folk understand clearly the evidence-based relationship between cancer and stress, and documents the world-wide clinical studies and research underpinning the 6 Phases of Cancer; as well as key remedies to help reverse each of these six distinct and interrelated phases.

## The 6 Phases of Cancer

### Phase

# 1

#### Inescapable Shock / Psycho-Emotional Trauma Experienced

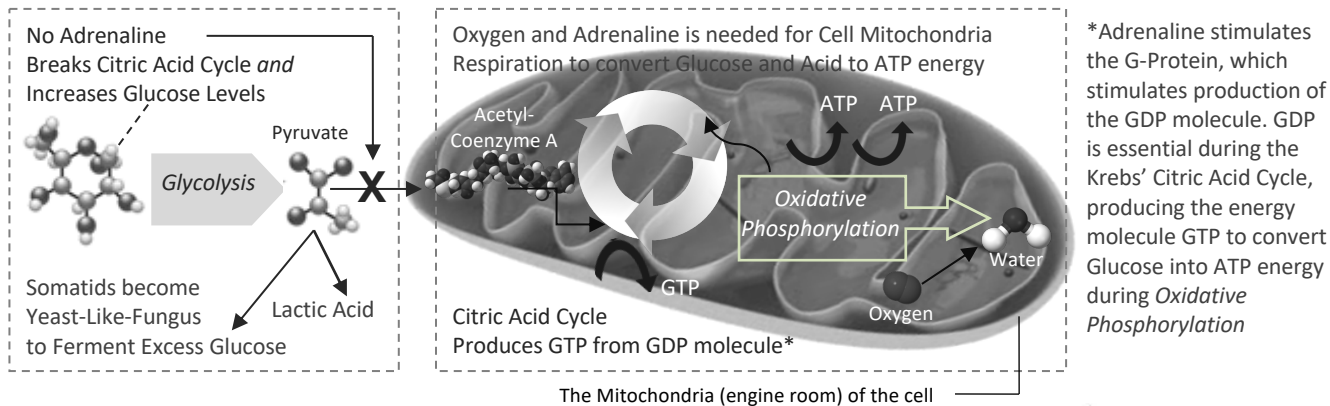
Phase 1 occurs approximately 18-24 months prior to the diagnosis of cancer. This is where the individual with cancer experiences an Inescapable Shock or acute psycho-emotional trauma, affecting deep sleep and the production of melatonin within the body. Melatonin is necessary for inhibiting cancer cell growth and is the primary hormone responsible for regulating the immune system; in particular production of interleukin 2 (IL-2) which governs white blood cell immune activity and protects against microbial infection. Without enough melatonin due to prolonged psycho-emotional stress, cancer cells thrive. As discovered by Dr Ryke Geerd Hamer every cancer has a specific psycho-emotional cause; whereby a part of the emotional reflex centre in the brain is damaged as a result of the prolonged psycho-emotional trauma. And as each part of the emotional reflex centre in the brain controls and is connected to a different organ of the body, as this emotion centre breaks down experiencing necrosis, so does the organ it controls leading to cancer.

#### Stress Depletes Adrenaline Breaking the Cell's (Krebs) Citric Acid Cycle, Causing the Cell to Ferment Rising Glucose Levels

During phase 2, elevated stress hormone cortisol levels deplete all-important adrenaline (epinephrine) levels. There are limited reserves of adrenaline in the body and when an individual is under constant psycho-emotional stress these reserves are depleted quickly. While insulin is used to transport glucose into cells, it is adrenaline which is critical for cell respiration and for converting this glucose in the cell into ATP energy for the body and for healthy cell division [which occurs via the metabolic pathway known as Oxidative Phosphorylation and via the Krebs' Citric Acid Cycle of the mitochondria of the cell]. Without adrenaline to stimulate the G-Protein to stimulate production of the GDP molecule [which is essential for mitochondrial cell respiration and glucose conversion] the cell's Krebs' Citric Acid Cycle and Oxidative Phosphorylation metabolic pathway is broken and the cell is forced to ferment glucose instead as a means to obtain [smaller amounts of] ATP energy [via the process known as Glycolysis], which creates lactic acid in the cell and a low pH environment.

### Phase

# 2



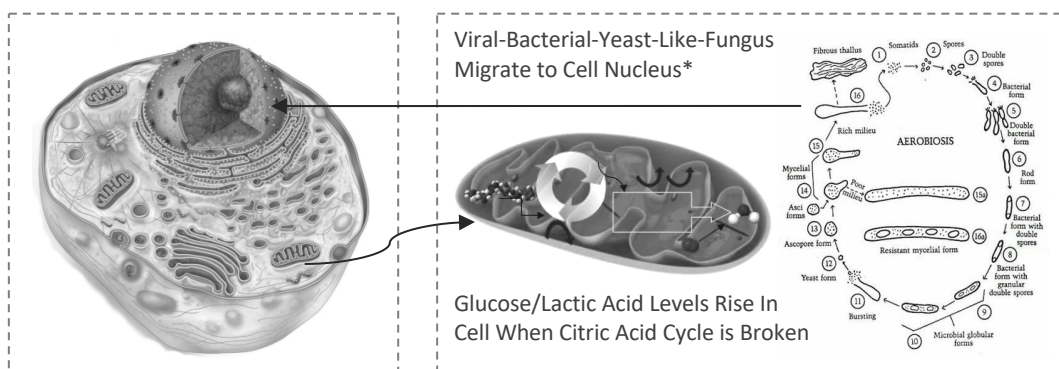
## Phase

Somatids Pleomorphise into Yeast-Like-Fungus to Ferment Excess Glucose and Lactic Acid in Cells, Causing Cell Nucleus DNA Mutation & Cancer

# 3

During phase 3, somatids (tiny microorganisms necessary for life) that live in our body pleomorphise [or change] into yeast-like-fungus to ferment excess glucose and lactic acid in cells. In a healthy person, somatids are limited to 3 stages in their life cycle – somatid, spore, double spore. However, in a highly acidic low pH lactic acid environment, somatids pleomorphise into a further 13 stages. These stages include viral-bacterial-yeast-like-fungus forms which ferment excess glucose and lactic acid in the cell. These fungal pathogenic forms then migrate to the cell nucleus to reproduce, releasing acidic waste products called “mycotoxins”, inhibiting cell DNA repair and inhibiting the all-important tumor suppressor genes. Without the tumor suppressor genes [namely p53] to regulate cell death (apoptosis) when the cell has mutated beyond repair, the cell lives on and ‘cell-growth regulating’ proto-oncogenes turn into oncogenes, causing normal cells to mutate into cancer cells.

\*Viral-Bacterial-Yeast-Like-Fungus release acidic waste products called *Mycotoxins* into the cell nucleus, inhibiting cell DNA repair and inhibiting tumor suppressor genes causing cell mutation and cancer



Depleted Adrenaline Depletes Dopamine and Tryptophan Levels Resulting in Niacin Deficiency, Breaking (Krebs) Citric Acid Cycle

## Phase

# 4

During phase 4, depleted adrenaline (epinephrine) levels cause a depletion of dopamine in the brain. Adrenaline is made by dopamine, and as more and more dopamine is used up during stress, the amino-acid tryptophan creates serotonin to offset depressed mood. This subsequently results in a depletion of tryptophan which is needed to synthesize niacin/niacinamide (vitamin B3)

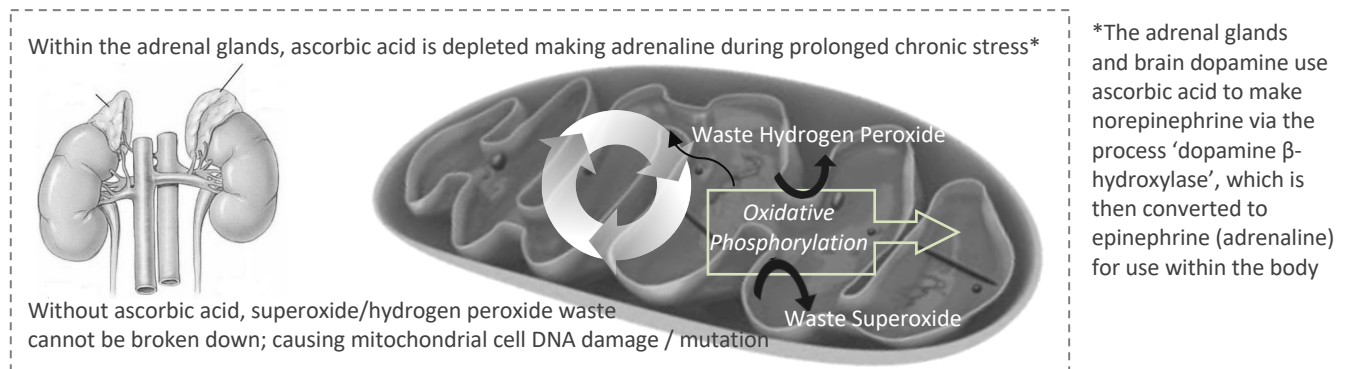
for cell respiration. Niacin/niacinamide is converted by tryptophan into NAD coenzymes which are subsequently used by the Krebs' Citric Acid Cycle in the mitochondria of the cell for glucose conversion, cell respiration and creation of ATP energy. Without tryptophan and niacin/niacinamide, the Krebs' Citric Acid Cycle / Oxidative Phosphorylation metabolic pathway is broken.

## Phase

Depleted Adrenaline and High Stress Cortisol Leads to Vitamin C Deficiency, Causing Cell Mitochondria DNA Mutation & Cancer

# 5

During phase 5, depleted adrenaline (epinephrine) levels cause a depletion of ascorbic acid (vitamin c) in the adrenal glands. Ascorbic acid is the main ingredient used by dopamine to make noradrenaline (norepinephrine) which is then converted to adrenaline. During prolonged chronic stress more and more adrenaline is pumped out and then depleted, meaning more and more ascorbic acid is used up in the creation of adrenaline. During chronic stress the adrenal glands also release ascorbic acid into the body to diminish the stressful impact of adrenaline [and other stress hormones] on the heart and blood pressure systems. Ascorbic acid is essential for preventing cell DNA damage caused by "oxidative stress", converting oxygen waste products 'superoxide' and 'hydrogen peroxide' into oxygen and water within the cell mitochondria during Oxidative Phosphorylation. The loss of ascorbic acid thereby increases cell mitochondrial DNA damage and cell mutation.



Prolonged Stress Results in a Subconscious Wanting to Die, Which Shuts Down the Immune System enabling Fungus & Cancer to Grow

## Phase

# 6

During phase 6, the immune system is shut down by a subconscious wanting to die, caused by elevated stress hormone cortisol levels depleting serotonin and dopamine levels in the brain that cause internal depression. As revealed by God, an individual experiencing Inescapable Shock and prolonged chronic stress often feels tired of life and deep down wants out of the never-ending struggle and pain of life, sending subliminal messages to the immune system to shut down. This occurs at the subconscious level where the immune system receives orders to stop production of interleukin 2-producing T cells, B cells, natural killer cells, macrophages and neutrophils. Without immune system cells, viral-bacterial-yeast-like-fungus that have pleomorphised within cells continue to grow and newly created cancer cells continue to multiply.

# The 1<sup>st</sup> Phase of Cancer



## Phase

# 1

### Inescapable Shock / Psycho-Emotional Trauma Experienced

Phase 1 occurs approximately 18-24 months prior to the diagnosis of cancer. This is where the individual with cancer experiences an Inescapable Shock or acute psycho-emotional trauma, affecting deep sleep and the production of melatonin within the body. Melatonin is necessary for inhibiting cancer cell growth and is the primary hormone responsible for regulating the immune system; in particular production of interleukin 2 (IL-2) which governs white blood cell immune activity and protects against microbial infection. Without enough melatonin due to prolonged psycho-emotional stress, cancer cells thrive. As discovered by Dr Ryke Geerd Hamer every cancer has a specific psycho-emotional cause; whereby a part of the emotional reflex centre in the brain is damaged as a result of the prolonged psycho-emotional trauma. And as each part of the emotional reflex centre in the brain controls and is connected to a different organ of the body, as this emotion centre breaks down experiencing necrosis, so does the organ it controls leading to cancer.

## The Theory

Over the past decades, a number of licensed medical practitioners working in the field of oncology have discovered cancer is preceded by a specific emotional trauma, occurring approximately 2 years prior to the diagnosis of cancer. Two of these practitioners include Dr W Douglas Brodie, founder of the Reno Integrative Medical Center in Nevada, USA and Dr Ryke Geerd Hamer, a former German physician and founder of German New Medicine. Both of these practitioners claim to have examined thousands of cancer patients in reaching this conclusion. More specifically, Dr Ryke Geerd Hamer proposes that each cancer in the body has a different emotional cause which he has identified; in other words the emotional cause for cancer of the left breast is different to that of the right breast and to cancer of the colon, etc. In my own personal experience in treating hundreds of cancer patients to heal the emotional and psychological cause of their disease, it has been my observation that Dr Ryke Geerd Hamer's proposed theory that each cancer has a different and very specific psycho-emotional cause is 100% accurate. For example, I always find a woman presenting with cancer of the left breast has [in line with Dr Hamer's theory] experienced a psychological and emotional conflict / trauma approximately 2 years prior to the diagnosis of cancer involving the "mother, child or home". Similarly, I always find a woman presenting with uterine cancer has experienced a "sexual conflict" 2 years prior to the diagnosis of cancer, and so on. On a personal level, my own mother [who was diagnosed with cancer of the left breast in 1992] experienced a psycho-emotional trauma 2 years prior in 1990 involving the death of her mother, in line with Dr Hamer's theory. I remember her telling me at the time she felt like a zombie for many months. As is typical with patients I see, my mother had a tendency to over-react to most difficulties in life and was always highly stressed, and it is this hypersensitivity to life's stressors that makes one susceptible to cancer. Dr W Douglas Brodie reveals it is not the stressful event that causes cancer, but our inability to cope with life stress.

Dr W Douglas Brodie: "In dealing with many thousands of cancer patients over the past 28 years, it has been my observation that there are certain personality traits present in the cancer-susceptible individual. These traits are as follows: 1. Being highly conscientious, caring, dutiful, responsible, hard-working, and usually of above average intelligence. 2. Exhibits a strong tendency toward carrying other people's burdens and toward taking on extra obligations, and often "worrying for others." 3. Having a deep-seated need to make others happy. Being a "people pleaser" with a great need for approval. 4. Often lacking closeness with one or both parents, which sometimes, later in life, results in lack of closeness with spouse or others who would normally be close. 5. Harbours long-suppressed toxic emotions, such as anger, resentment and / or hostility. The cancer-susceptible individual typically internalizes such emotions and has great difficulty expressing them. 6. Reacts adversely to stress, and often becomes unable to cope adequately with such stress. Usually experiences an especially

damaging event about 2 years before the onset of detectable cancer. The patient is not able to cope with this traumatic event or series of events, which comes as a "last straw" on top of years of suppressed reactions to stress. 7. Has an inability to resolve deep-seated emotional problems/conflicts, usually beginning in childhood, often even being unaware of their presence. Typical of the cancer-susceptible personality, as noted above, is the long-standing tendency to suppress "toxic emotions", particularly anger. Usually beginning in childhood, this individual has held in their hostility and other unacceptable emotions. More often than not, this feature of the affected personality has its origins in feelings of rejection by one or both parents. Whether these feelings of rejection are justified or not, the individual perceives this rejection as real, and this results in a lack of closeness with the "rejecting" parent, followed later in life by a lack of closeness with spouses and others with whom close relationships would normally develop. Those at the higher risk for cancer tend to develop feelings of loneliness as a result of their having been deprived of affection and acceptance earlier in life, even if this is only their perception. They have a tremendous need for approval and acceptance, and develop a very high sensitivity to the needs of others while suppressing their own emotional needs.

They become the "caretakers" of the world, showing great compassion and caring for others, and will go out of their way to look after others. They are very reluctant to accept help from others, fearing that it may jeopardize their role as the caretaker. Throughout their childhood they have been typically taught "not to be selfish", and they take this to heart as a major lifetime objective. All of this is highly commendable in our culture, but must be somehow modified in the case of the cancer patient. A distinction needs to be made here between the "care-giving" and the "care-taking" personality. There is nothing wrong with care-giving, of course, but the problem arises when the susceptible individual derives their entire worth, value and identity from their role as "caretaker". If this very important shift cannot be made, the patient is stuck in this role, and the susceptibility to cancer greatly increases. As already stated, a consistent feature of those who are susceptible to cancer appears to be that they "suffer in silence", and bear their burdens without complaint. These burdens of their own as well as the burdens of others weigh heavily upon these people through a lifetime of emotional suppression. The carefree extrovert, on the other hand, seems to be far less vulnerable to cancer than the caring introvert described above.

How one reacts to stress appears to be a major factor in the larger number of contributing causes of cancer. Most cancer patients have experienced a highly stressful event, usually about 2 years prior to the onset of detectable disease. This traumatic event is often beyond the patient's control, such as the loss of a loved one, loss of a business, job, home, or some other major disaster. The typical cancer personality has lost the ability to cope with these extreme events, because his/her coping mechanism lies in his/her ability to control the environment. When this control is lost, the patient has no other way to cope. Major stress causes suppression of the immune system, and does so more overwhelmingly in the cancer-susceptible individual than in others. Thus personal tragedies and excessive levels of stress appear to combine with the underlying personality described above to bring on the immune deficiency which allows cancer to thrive."

Dr Ryke Geerd Hamer discovered a connection between cancer and unresolved psychological / emotional conflict through first-hand experience. His son was murdered and soon after he developed testicular cancer, which he identifies as the result of a "loss conflict". From this experience, and as chief of internal medicine in a gynecology-oncology clinic at Munich University, he was able to interview and examine the records of thousands of cancer patients. His research led him to identify the presence of concentric rings in the emotional reflex centre of the brain as being evidence of the psycho-emotional trauma on the brain itself, which he called "Hamer Herds". He proposes the location of the Hamer Herd (HH) on the brain which is seen through a CT scan, is like a map, which to the trained

practitioner can reveal the precise disease and its organ-location in the body. Dr Hamer offers images such as the one below, as evidence of these concentric rings or Hamer Herds.



Dr Ryke Geerd Hamer: "Every cancer or cancer-like disease originates with a very difficult highly acute, dramatic and isolating shock. The experience of shock is simultaneous or virtually simultaneous on three levels: 1. the psyche 2. the brain 3. the organ. The development of the conflict determines a specific development of the HH (Hamer Herd) in the brain and of the cancer or cancer-equivalent disease in the organ. There are very specific signs which clearly distinguish the ordinary conflicts and problems in our daily lives. From the very first moment of a DHS (psycho-emotional trauma), you would experience continuous stress on the sympathetic nervous system. The symptoms would include cold hands and/or feet, loss of appetite, weight loss, sleeplessness and dwelling day and night on the conflict content. This situation will only change when the conflict has been resolved. In contrast to normal everyday problems, we see the patient falling into a lasting stress phase that will cause specific symptoms and a growing cancer. The HH (Hamer Herd) in the brain, which is immediately visible, shows that the patient's psyche has very precise, defined symptoms that cannot be overlooked. I discovered the ontogenetic system of tumors and cancer-equivalents after observing about 10,000 cases. I worked absolutely empirically, like a good scientist should. I documented all the collected cases and the CT scans of the brain with their histological findings. Only after I had put them all together and compared them did I see that there was a system.

I didn't really occupy myself with this until 1978. I was a doctor of internal medicine and had worked in university clinics for fifteen years, five of them as a professor. Then a terrible thing happened: while asleep on a boat, my son Dirk was shot, for no reason, by a madman, an Italian prince. This was a terrible shock for me, sudden and unexpected, and I was powerless to react. Every day events or conflicts don't usually catch us so "off guard". We generally have a chance to anticipate the normal conflicts that we face in life, but the conflicts we are unable to prepare for and which cause this helplessness and inability to react, create, in essence, a panic shock. We call these biological conflicts. In 1978 I developed testicular cancer from such a biological conflict, a so-called "loss conflict". Since I had never been seriously ill, I wondered if my condition had anything to do with the death of my son. Three years later, as chief of internal medicine in a gynecology-oncology clinic at Munich University, I had the opportunity to study female patients with cancer and to compare my findings to see if their mechanism was the same as mine; if they too had experienced such a terrible shock. I found that all of them, without exception, had experienced the same type of biological conflict as I had. They were able to recollect the shock, the resulting sleeplessness, weight loss, cold hands and the beginning of tumor growth.

There is at present a movement to divide medicine into organic medicine and psychological medicine, or psychotherapy. When a doctor states that there is no organic cause, he is giving the psychotherapist a free hand to treat these 'clean' psychological diseases. Such division is absurd in the eyes of a practitioner of the



German New Medicine, because illness cannot be divided and parcelled out. The psyche, brain and organ are three levels of the same organism and the course of events on them is always synchronous.”



[Dr Ryke Geerd Hamer]

Dr Hamer proposes a person who experiences the onset of detectable cancer has experienced a “biological conflict” or Inescapable Shock that causes subsequent organ-necrosis and tumour cell growth. And this has been validated in research conducted by Madelon Visintainer, now Associate Professor at Yale University School of Medicine, where rats receiving mild in-escapable shock had a significantly higher rate of tumour progression. In my own experience of treating hundreds of cancer patients, this biological conflict or Inescapable Shock serves as the “trigger event” for cancer to develop within the body. The cancer-susceptible personality is already highly stressed prior to this trigger event, which is like the straw that breaks the camel’s back, destabilizing the body’s natural homeostasis and causing cancer. What I also found was the trigger event has a common psycho-emotional theme with previously unresolved conflicts the cancer patient has experienced earlier on in their life, commonly during childhood, as well as during past lives. In one notable case, cancer patient Dr Suzanne Friedman of San Francisco USA [who has given permission for her experience to be shared] presented with stage IV inoperable lung cancer, having been given 7 months to live. According to Dr Hamer the psycho-emotional cause for lung cancer is “fear of dying or suffocation, including fear for someone else”. In line with Dr Hamer’s theory, Dr Friedman experienced a relationship trauma 2 years prior to the onset of detectable cancer where the psycho-emotional conflict she could not resolve was feeling suffocated. Using hypnosis and past life regression, the cancer present within Dr Friedman’s lungs led us to earlier experiences in her childhood where she felt suffocated and to a past-life where [as a mother of two children] she was gassed in a concentration camp in Nazi Germany, experiencing fear of death and suffocation. It was this past-life unresolved event that was the most highly charged, being more stressful than the trigger event itself. And this is not uncommon in cancer patients I see, that the trigger event is less emotionally charged than previously unresolved conflicts. All psycho-emotional conflicts were resolved in this case and Dr Friedman became cancer-free within weeks. As is common with cancer patients I see, the trigger event presents to help the patient resolve previously unresolved conflicts involving the same psycho-emotional theme. Below is a list of conflicts Dr Ryke Geerd Hamer proposes serves as the trigger event and cause for each different type of cancer in the body.

- ❖ ADRENAL CORTEX: Wrong Direction. Gone Astray
- ❖ BLADDER: Ugly Conflict. Dirty Tricks
- ❖ BONE: Lack of Self Worth. Inferiority Feeling
- ❖ BRAIN TUMOR: Stubbornness. Refusing to Change Old Patterns. Mental Frustration  
[Dr Hamer does not propose a conflict for brain tumour. The above is Louise Hay’s proposed cause.]
- ❖ BREAST MILK GLAND: Involving Care or Disharmony
- ❖ BREAST MILK DUCT: Separation Conflict
- ❖ BREAST LEFT: Conflict concerning Child, Home or Mother
- ❖ BREAST RIGHT: Conflict with Partner or Others
- ❖ BRONCHIOLES: Territorial Conflict
- ❖ CERVIX: Severe Frustration
- ❖ COLON: Ugly Indigestible Conflict
- ❖ ESOPHAGUS: Cannot Have It or Swallow It
- ❖ GALL BLADDER: Rivalry Conflict
- ❖ HEART: Perpetual Conflict
- ❖ INTESTINES: Indigestible Chunk of Anger
- ❖ KIDNEYS: Not wanting to Live. Water or Fluid Conflict
- ❖ LARYNX: Conflict of Fear and Fright
- ❖ LIVER: Fear of Starvation

- ❖ LUNGS: Fear of Dying or Suffocation, including Fear for Someone Else
- ❖ LYMPH GLANDS: Loss of Self-Worth associated with the Location
- ❖ MELANOMA: Feeling Dirty, Soiled, Defiled
- ❖ MIDDLE EAR: Not being able to get some Vital Information
- ❖ MOUTH: Cannot Chew It or Hold It
- ❖ PANCREAS: Anxiety-Anger Conflict with Family Members. Inheritance
- ❖ PROSTATE: Ugly Conflict with Sexual Connections or Connotations
- ❖ RECTUM: Fear of Being Useless
- ❖ SKIN: Loss of Integrity
- ❖ SPLEEN: Shock of being Physically or Emotionally Wounded
- ❖ STOMACH: Indigestible Anger. Swallowed Too Much
- ❖ TESTES / OVARIES: Loss Conflict
- ❖ THYROID: Feeling Powerless
- ❖ TUMOR (IN LOCATION): Nursing Old Hurts and Shocks. Building Remorse  
[Dr Hamer does not propose a conflict for tumour. The above is Louise Hay's proposed cause.]
- ❖ UTERUS: Sexual Conflict

While most people cope with stress, those susceptible to cancer appear to be highly vulnerable to life's stresses and trauma, and feel unable to cope when life throws a curve-ball their way. These people are perfectionists and live in fear of conflict, stress, trauma and loss and are deeply frightened of negative events. And when faced with a highly stressful or traumatic event they have not anticipated, which inevitably happens during their life, react adversely and are unable to cope. They experience Inescapable Shock and remain deeply affected by the experience. When faced with a major trauma, the cancer personality feels trapped and unable to escape from the memory of the traumatic experience and the painful feelings [of anger, hate, resentment and/or grief] associated with the experience. Stress hormone cortisol levels skyrocket and remain at high levels. High stress levels generally mean a person cannot sleep well and cannot produce enough melatonin which is produced during deep sleep usually between the hours of 1am and 3am in the morning. Melatonin is the primary hormone responsible for regulating the immune system, and when there is not enough melatonin, production of IL-1 (Interleukin 1) and IL-2 (Interleukin 2) is diminished. Interleukin 1 protects against infection and Interleukin 2 regulates the activities of white blood cells [including T cells, B cells, neutrophils, macrophages and natural killer cells] responsible for immunity. Interleukin 2 is part of the body's natural response to microbial infection, and when there is insufficient levels of Interleukin 2, stress-induced viral-bacterial-yeast-like-fungus that have pleomorphised in the body [as described in Phase 3] are now free to invade normal cells; damaging cell DNA through the release of "mycotoxins" within the cell nucleus, causing proto-oncogenes to mutate into oncogenes, and inhibiting tumor suppressor genes [notably p53] which results in normal cells mutating into cancer cells. Hence the American Cancer Society states: "Melatonin has been shown to slow or stop the growth of several types of cancer cells when studied in the laboratory" and why the National Cancer Institute Office of CAM states: "Both melatonin and chronotherapy have been studied for many years but, despite largely positive findings, have not been brought into mainstream cancer therapy. We hope these presentations will contribute to re-invigorating activities focused on the examination of these and related approaches to cancer management."

Within the 1<sup>st</sup> Phase of Cancer the following sequence of events can be observed in the cancer patient:



## The Evidence

The evidence for Phase 1 of Cancer can be broken down into the following components: a) the link between cancer and the suppression of toxic emotions [including anger, hate, resentment, unforgiveness and complicated grief], b) the link between cancer and elevated stress hormone cortisol levels, c) the link between stress and sleeplessness, d) the link between lack of deep sleep and low melatonin levels, e) the link between low melatonin levels and reduced immunity, specifically on production of IL-1 (Interleukin 1) and IL-2 (Interleukin 2), f) the link between low melatonin levels and tumour cell growth, g) the link between low levels of IL-2 (interleukin 2) and tumour cell growth, h) the link between low levels of IL-2 (interleukin 2) and increased microbial infection in the human body.

### ➤ Evidence of the Link Between Cancer and the Suppression of Toxic Emotions

1. Extreme suppression of anger was the most commonly identified characteristic of 160 breast cancer patients who were given a detailed psychological interview and self-administered questionnaire in a study conducted by the King's College Hospital in London, as reported by the Journal of Psychosomatic Research. "As part of an interdisciplinary study of breast cancer, psychological investigation of a consecutive series 160 women admitted to hospital for breast tumour biopsy was carried out by means of detailed structured interviews and standard tests. Interviews and testing were conducted on the day before operation, without knowledge of the provisional diagnosis. Information obtained from patients was verified in almost all cases by separate interviews with husbands or close relatives. Present results are based on statistical comparisons between 69 patients found at operation to have breast cancer and a control group comprising the remaining 91 patients with benign breast disease. Our principal finding was a significant association between the diagnosis of breast cancer and a behaviour pattern, persisting throughout adult life, of abnormal release of emotions. This abnormality was, in most cases, extreme suppression of anger and, in patients over 40, extreme suppression of other feelings." [<http://www.sciencedirect.com/science/article/pii/002239975900628>]
2. As reported by the College of Nursing, University of Tennessee: "Extremely low anger scores have been noted in numerous studies of patients with cancer. Such low scores suggest suppression, repression, or restraint of anger. There is evidence to show that suppressed anger can be a precursor to the development of cancer, and also a factor in its progression after diagnosis." [<http://www.ncbi.nlm.nih.gov/pubmed/11037954>]
3. A landmark study conducted by Aarhus University of Denmark and the University of California found children born in Sweden and Denmark between 1968 and 2007 had a 10% greater chance of developing childhood cancer if they experienced the loss of a close relative (bereavement). "All live-born children born in Denmark between 1968 and 2007 (n=2 729 308) and in Sweden between 1973 and 2006 (n=3 395 166) were included in this study. A total of 1 505 938 (24.5%) children experienced bereavement at some point during their childhood and 9823 were diagnosed with cancer before the age of 15 years. The exposed children had a small (10%) increased risk of childhood cancer." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3664350/>]
4. In a study conducted by the World Health Organization, 6284 Jewish Israelis who lost an adult son in the Yom Kippur War or in an accident between 1970 and 1977 were followed over a 20 year period to compare the incidence of cancer in the bereaved group compared to non-bereaved members of the population. The study concluded: "There was an increased incidence of lymphatic and hematopoietic malignancies, among parents of accident victims and among war-bereaved parents, as well as for melanomas. Accident-bereaved parents also had an increased risk of respiratory (lung) cancer." [<http://www.ncbi.nlm.nih.gov/pubmed/11029995>]
5. 1,088 women with cancer were seen over a 4.5 year period at the Cancer Centre of the Greek Social Security Department in Athens, Greece. "The authors present their results as far as psychological stress influences the development of cancer of the breast in 813 patients (Group A) and in 685 women who did not have cancer of the breast (Group B). They were able to show that Group A had a positive correlation which was statistically very significant with the following parameters: the death of a much-loved person; the negative behaviour of the husband; an unexpected change in life style; continual conflicts in the family; financial problems; unsatisfactory sex life; consultations with a psychiatrist and allergy. There was a positive correlation which was statistically significant with the parameters: disappointment in sentiment; a lowering in life style; a family history of cancer of the breast; hypertension; late start in the menarche and the onset of the menopause. The authors conclude that they believe that it is useful to look at all the factors that are known as risks for cancer of the breast, including the influence of psycho-traumatic factors." [<http://www.ncbi.nlm.nih.gov/pubmed/3819354>]

6. The University of Helsinki, Finland conducted a study of 10,808 women to discover whether stressful life events preceded the onset of cancer. "The authors prospectively investigated the relation between stressful life events and risk of breast cancer among 10,808 women from the Finnish Twin Cohort. Life events and breast cancer risk factors were assessed by self-administered questionnaire in 1981. A national modification of a standardized life event inventory was used, examining accumulation of life events and individual life events and placing emphasis on the 5 years preceding completion of the questionnaire. Through record linkage with the Finnish Cancer Registry, 180 incident cases of breast cancer were identified in the cohort between 1982 and 1996. Independently of total life events, – divorce/separation, death of a husband, and death of a close relative or friend were all associated with increased risk of breast cancer. The findings suggest a role for life events in breast cancer etiology through hormonal or other mechanisms." [http://www.ncbi.nlm.nih.gov/pubmed/12615606]
7. Funded by the California Breast Cancer Research Program, Stanford University conducted a 4 year study to confirm earlier findings that emotional expression extended cancer survival. "By 3 years from study entry, all but 2 women with more constrained anger have died--compared with 6 women, who express no constrained anger or only express short moments of it, still living at 7 years post-study entry. The mean survival time was, thus, doubled for women who do not constrain anger (3.7 years compared with 1.8)". [http://cbcrp.org.127.seekdotnet.com/research/PageGrant.asp?grant\_id=9]
8. A major study involving 847 US women diagnosed with invasive breast cancer were studied from 1985-1994 by the California Department of Health Services and National Cancer Institute to see whether emotional expression and a fighting spirit affected cancer survival rates. "Patients who reported low levels of emotional expression in conjunction with low levels of emotional support experienced worse survival than women who reported high levels of both. Although similar risk relations were evident among Blacks, Whites, and women with late stage disease, the risk was more pronounced among women with early stage tumors. These patients had a nearly fourfold risk of dying from breast cancer if they reported low levels of both emotional expression and emotional support when compared with patients with early stage tumors who reported high levels of both." [http://aje.oxfordjournals.org/content/152/10/940.full]
9. The Department of Psychiatry, UCLA School of Medicine found psychological intervention lowered distress and increased coping abilities in cancer patients and significantly increased cancer survival. Six years after the study, 10 of 34 patients in the control group who were not given psychological intervention had died, compared to only 3 of 34 patients given psychological intervention. "We evaluated recurrence and survival for 68 patients with malignant melanoma who participated in a 6-week structured psychiatric group intervention 5 to 6 years earlier, shortly after their diagnosis. For control patients, there was a trend for recurrence (13/34) and a statistically significant greater rate of death (10/34) than for experimental patients (7/34 and 3/34, respectively)." [http://www.ncbi.nlm.nih.gov/pubmed/8357293?dopt=Abstract]
10. The Ontario Cancer Institute / Princess Margaret Hospital conducted a 5 year 'Prospective, longitudinal study of the relationship of psychological work to duration of survival in patients with metastatic cancer'. They found a strong association between longer survival and psychological factors related to the involvement of cancer patients in psychological self-help activities. "Median survival of the 22 subjects was 2.25 times that predicted by the oncology panel (with six subjects still alive at the time of writing)." [http://www.healingjourney.ca/article.html]
11. Retired Clinical Professor of Surgery at Yale Medical School, Dr Bernie Siegel: "I have collected 57 extremely well documented so-called cancer miracles. At a certain particular moment in time they decided that the anger and the depression were probably not the best way to go, since they had such little time left. And so they went from that to being loving, caring, no longer angry, no longer depressed, and able to talk to the people they loved. These 57 people had the same pattern. They gave up, totally, their anger, and they gave up, totally, their depression, by specifically a decision to do so. And at that point the tumors started to shrink." [http://berniesiegelmd.com/]
12. Researchers at the Department of Psychiatry and Behavioral Sciences, Stanford University, studied 91 women with metastatic breast cancer and found women with high repression of emotions and high anxiety scores had increased stress hormone cortisol levels [observed as a flatter diurnal cortisol slope] which they had found in earlier studies was linked to increased mortality. "When compared with self-assured and nonextreme groups, the represser and high-anxious groups had a significantly flatter diurnal slope. Recently published data from the authors' laboratory demonstrated that flatter diurnal cortisol slopes were a risk factor for early mortality in women with metastatic breast cancer." [http://www.ncbi.nlm.nih.gov/pubmed/15546233]

➤ Evidence of the Link Between Cancer and Elevated Stress Hormone Cortisol Levels

13. The University of Wisconsin Medical School studied 17 women with breast cancer and 31 women without breast cancer and found those with breast cancer had significantly higher cortisol levels than the control group of woman. "Women with metastatic breast cancer had significantly flatter diurnal cortisol rhythms than did healthy controls. Patients with greater disease severity showed higher mean cortisol levels, smaller waist circumference, and a tendency toward flatter diurnal cortisol rhythms." [<http://www.ncbi.nlm.nih.gov/pubmed/15219660>]
14. The Department of Psychological and Brain Sciences, University of Louisville studied 57 lung cancer patients and discovered higher cortisol levels (a flattening of the diurnal cortisol slope) predicted early death. "The diurnal cortisol slope predicted subsequent survival over three years. Early mortality occurred among patients with higher slopes, or relatively "flat" rhythms indicating lack of normal diurnal variation. Cortisol slope also predicted survival time from initial diagnosis ( $p=.012$ ). After adjustment for possible confounding factors, diurnal slope remained a significant, independent predictor of survival. Flattening of the diurnal cortisol rhythm predicts early lung cancer death." [<http://www.ncbi.nlm.nih.gov/pubmed/22884416>]
15. The University of Louisville, School of Medicine studied 104 metastatic breast cancer patients and discovered higher cortisol levels (flatter rhythms) predicted early death. "Cortisol slope predicted subsequent survival up to 7 years later. Earlier mortality occurred among patients with relatively "flat" rhythms, indicating a lack of normal diurnal variation. Flattened profiles were linked with low counts and suppressed activity of (natural killer) NK [immune] cells. After adjustment for each of these and other factors, the cortisol slope remained a statistically significant, independent predictor of survival time. NK cell count emerged as a secondary predictor of survival." [<http://www.ncbi.nlm.nih.gov/pubmed/10861311>]
16. The Oral Oncology Center, School of Dentistry of Araçatuba, Brazil compared cortisol levels in 34 oral cancer patients to 86 [non-cancer] control subjects. "The plasma and salivary cortisol levels were significantly higher in patients with oral SCC (squamous cell carcinoma) compared with all groups. These results indicate a dysregulation of cortisol secretion in patients with oral cancer and suggest that this hormone can be a biomarker associated with the disease's clinical status." [<http://www.ncbi.nlm.nih.gov/pubmed/22734006>]
17. A study conducted by the National Institutes of Health tested the cortisol levels of 177 women suspected of having ovarian cancer and found significantly higher cortisol levels in those who tested positive for ovarian cancer. "Women ( $n = 177$ ) with suspected ovarian cancer completed questionnaires and collected salivary cortisol 3x daily for 3 consecutive days before surgery. One hundred women were subsequently diagnosed with ovarian cancer and 77 with benign disease. In addition, healthy women ( $n = 33$ ) not scheduled for surgery collected salivary cortisol at the same time points. Ovarian cancer patients demonstrated significantly elevated nocturnal cortisol ( $P = .022$ ) and diminished cortisol variability ( $P = .023$ ) compared with women with benign disease and with healthy women (all  $P$  values  $<.0001$ )." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3118555/>]
18. A study of 31 breast cancer patients conducted by the Helen Dowling Institute for Biopsychosocial Medicine, The Netherlands found a significant increase in stress hormone cortisol levels in those with cancer compared to healthy controls. "Hormones of the hypothalamic-pituitary-adrenal system were studied in 31 patients with early stage breast cancer and patients with metastatic breast cancer. Both groups received tamoxifen as first-line treatment. As a control group 15 age-matched healthy women participated in the study. The results showed that breast cancer patients had significant elevations in basal cortisol levels compared to controls. Metastatic breast cancer patients had higher cortisol levels than early stage breast cancer patients." [<http://www.ncbi.nlm.nih.gov/pubmed/8844875>]
19. The Department of Biomedical and Diagnostic Sciences, University of Tennessee grafted pancreatic cancer tissue into mice and found mice exposed to psychological stress had increased stress hormone cortisol levels and a significantly higher rate of cancer growth compared to mice in this group not exposed to psychological stress. "Pancreatic cancer has a poor prognosis and is associated with high levels of psychological stress that may adversely affect clinical outcomes. Using a mouse model of social stress, we have tested the hypothesis that psychological stress promotes the progression of pancreatic cancer xenografts via neurotransmitter-induced activation of multiple pathways. Psychological stress significantly promoted xenograft growth and increased systemic and tumor levels of noradrenalin, adrenalin, cortisol, VEGF and cAMP." [<http://www.ncbi.nlm.nih.gov/pubmed/22072614>]

➤ Evidence of the Link Between Stress and Sleeplessness

20. In a study reported in the journal of Psychosomatic Medicine comprising of 31 insomniacs (poor sleepers) and 31 good sleepers, researchers found: "During the year their insomnia began, chronic insomniacs experienced a greater number of stressful life events compared with previous or subsequent years and compared with good sleepers. In addition, among the life event categories assessed, insomniacs reported a greater number of undesirable events, particularly events related to losses and to ill health."  
[<http://www.psychosomaticmedicine.org/content/43/5/439.full.pdf+html>]
21. In a study of 367 outpatients with Post Traumatic Stress Disorder (PTSD), the University of Pittsburgh, School of Medicine found patients with more severe PTSD had greater sleep disturbance. "Sleep disturbances (SD) are a core clinical feature of PTSD. The goal of the study was to determine the influence of patient-related characteristics, disorder-related characteristics, and psychiatric comorbidity on the severity of SD in PTSD outpatients (n = 367) who were not recruited for a sleep study. Increased severity of SD (sleep disturbance) paralleled increasing overall PTSD severity." [<http://www.ncbi.nlm.nih.gov/pubmed/15730066>]
22. The Department of Psychology, University of North Texas conducted a study of 772 people with and without insomnia to determine the prevalence of associated clinical anxiety and depression. "People with insomnia had greater depression and anxiety levels than people not having insomnia and were 9.82 and 17.35 times as likely to have clinically significant depression and anxiety, respectively. Increased insomnia frequency was related to increased depression and anxiety, and increased number of awakenings was also related to increased depression. These results reaffirm the close relationship of insomnia, depression, and anxiety, after rigorously controlling for other potential explanations for the relationship."  
[<http://www.ncbi.nlm.nih.gov/pubmed/16335332>]
23. In a study of 815 college students, researchers at the Department of Psychology, The University of Memphis found a significant increase in insomnia in those experiencing complicated grief. "As predicted, the rate of insomnia was significantly higher (22%) in the bereaved sample than in a nonbereaved comparison group (17%), a difference that was particularly pronounced in terms of middle insomnia."  
[<http://www.ncbi.nlm.nih.gov/pubmed/15802260>]
24. The Department of Psychology, University of California conducted a study of 5,692 subjects (including 3,711 with no mood or anxiety disorder, 327 with mood disorders only, 1,137 with anxiety disorders only, and 517 with coexisting mood and anxiety disorders) to determine the prevalence of insomnia. "Respondents with comorbid mood and anxiety disorders had significantly higher rates of severe insomnia complaints (42.1-62.8%) relative to the three other groups. Severe insomnia complaints were also significantly more prevalent in individuals with mood (25.2-45.6%) or anxiety disorders only (24.9-45.5%) relative to those with no disorder (12.4-24.3%)." [<http://www.ncbi.nlm.nih.gov/pubmed/23024435>]
25. A survey of 2,121 insomniac patients was conducted in France, Germany, Italy and the United Kingdom by the Hôpital Universitaire du Bocage, France to determine the primary cause/s of insomnia. "The most frequently cited causes of insomnia were stress, loneliness and bereavement. Insomnia was usually reported as chronic, and frequently as episodic. Frequently cited symptoms were poor sleep quality, interrupted sleep, early awakening, difficulties in getting to sleep and daytime fatigue."  
[<http://www.ncbi.nlm.nih.gov/pubmed/15291008>]
26. In a landmark study of 5,622 insomniacs in France by the Stanford Sleep Epidemiology Research Center, School of Medicine, Stanford University, researchers found the following: "A depressive disorder diagnosis was given in 10.8% of cases (mainly a major depressive disorder). An anxiety disorder diagnosis was given for 33.1% of insomnia complainers (an anxiety generalized disorder in about half the cases). In the majority of cases, the insomnia complaint is part of the symptomatology of a mental disorder, mainly an anxiety disorder." [<http://www.ncbi.nlm.nih.gov/pubmed/12386543>]
27. In a groundbreaking study of returning soldiers who completed the Post Traumatic Stress Disorder checklist from Iraq and Afghanistan, the Naval Medical Center San Diego, Department of Mental Health found 41% reported difficulty sleeping. "This study retrospectively reviewed records from current members of the U.S. military who had completed the PTSD Checklist (PCL) at 0 and 3-months after returning from deployments. Insomnia was the most commonly reported symptom of PTSD (post traumatic stress disorder) on the PCL and had the highest average severity scores. At initial screen, 41% of those who had been to Iraq or Afghanistan reported sleep problems." [<http://www.ncbi.nlm.nih.gov/pubmed/20968266>]

28. A study of returning combat soldiers conducted by the Psychiatry Continuity Service, Walter Reed National Military Medical Center, Maryland, found the following: "The objective of this study was to examine the relationships between combat related trauma, insomnia, and alcohol misuse. The author reviewed the standardized tests results from 39 active duty service members, all of whom had recent deployments to either Iraq or Afghanistan. The battery of self-test instruments assessed the effects of military trauma, anxiety, depression, alcohol use, and insomnia. Among the study subjects, the entire group reported significant sleep problems, with bedtime arousals impeding sleep initiation. Male subjects' reported an average AUDIT score of 8.62. Service members with higher trauma scores also reported greater misuse of alcohol. The high trauma scores also correlated with specific pre-sleep cognitive and somatic factors."  
[<http://www.ncbi.nlm.nih.gov/pubmed/23244556>]

➤ Evidence of the Link Between Lack of Deep Sleep and Low Melatonin Levels

29. The Cousins Center for Psychoneuroimmunology, University of California, studied the release of melatonin during sleep between alcoholics known to have sleep disorders and control subjects and found: "Coupled with prolonged sleep latency, alcoholics showed lower levels of melatonin during the early part of the night and a delay in the onset of the nocturnal plateau or peak value of melatonin as compared with control subjects. The nocturnal delay of melatonin correlated with prolonged sleep latency."  
[<http://www.ncbi.nlm.nih.gov/pubmed/14675809>]

30. The Department of Psychiatry, University of Göttingen studied 10 patients with chronic insomnia compared with 5 healthy control subjects and found a significant drop in melatonin production during sleep hours in insomniacs. "Plasma melatonin levels in the patient group tended to begin increasing earlier in the evening and were significantly lower during the middle of the night (peak value 82.5 +/- 26.5 pg/ml) than in the healthy controls (peak value 116.8 +/- 13.5 pg/ml). Among the patients, the most severely reduced nocturnal plasma melatonin levels were found in those patients with a history of sleep disturbance lasting for longer than five years. These results show that the circadian rhythm of melatonin secretion is disturbed in patients with chronic primary insomnia, and that the nocturnal plasma melatonin secretion is increasingly more affected the longer the patients are unable to maintain a regular sleep pattern."  
[<http://www.ncbi.nlm.nih.gov/pubmed/8750344>]

31. A similar study by the Department of Psychiatry and Psychotherapy, University Hospital of Freiburg compared the release of melatonin during sleep hours between 10 insomniacs and 10 healthy controls. "All subjects spent three consecutive nights in the sleep laboratory with polysomnography. Measurement of cortisol and melatonin (from 19:00 h to 09:00 h) was performed prior to and during the last laboratory night. Contrary to expectation, cortisol secretion did not differ between healthy controls and insomniac patients. On the other hand, nocturnal melatonin production was significantly diminished in insomniac patients."  
[<http://www.ncbi.nlm.nih.gov/pubmed/12467942>]

32. The Department of Human Biology, Zoological Institute, Christian-Albrechts-University studied the release of melatonin between 11 elderly poor-sleepers, 9 elderly good-sleepers and 10 younger good-sleepers and found: "Mean melatonin levels increased in young women (from 16.2 to 54.1 pg/mL) and older women (from 10.0 to 23.5 pg/mL), being lowest among the older poor sleepers (from 20:00 to 24:00 h,  $p < .05$  vs. young women). Older poor sleepers also showed a smaller increase in melatonin level from 17:00 to 24:00 h than older good sleepers (mean  $\pm$  SD: 7.0  $\pm$  9.63 pg/mL vs. 15.6  $\pm$  24.1 pg/mL,  $p = .013$ )."  
[<http://www.ncbi.nlm.nih.gov/pubmed/21929299>]

33. The Department of Internal Medicine, Stockholm Söder Hospital studied 8 patients with Fibromyalgia which is often associated with sleep disturbance and 8 healthy controls and found: "Most patients with fibromyalgic syndrome (FMS) complain of sleep disturbances, fatigue, and pain. The FMS patients had a 31% lower MT (melatonin) secretion than healthy subjects during the hours of darkness (MT AUC 2300-0700 h (mean +/- SEM): 1.70 +/- 0.17 vs 2.48 +/- 0.38 nmol/l). Also the s-MT (melatonin) peak value was significantly lower in the patient group: 0.28 +/- 0.03 vs 0.44 +/- 0.06 nmol/l)." [<http://www.ncbi.nlm.nih.gov/pubmed/9828904>]

34. The Dept of Neuropsychiatry, Akita University School of Medicine, Japan studied 10 Alzheimer's patients with disturbed sleep patterns and 10 healthy controls and found: "The SDAT (Alzheimer's) group showed a significantly higher degree of irregularities in actigraphically recorded rest-activity (R-A) rhythm during the 7-day baseline period compared with the ND (healthy control) group. The SDAT group simultaneously showed significantly reduced amplitude, larger variation of peak times, and diminished amount of total secretion in the melatonin secretion rhythm compared with the ND group. There were significantly positive

correlations between the severity of R-A rhythm disorder and the reduced amplitude as well as diminished amount of total melatonin secretion." [<http://www.ncbi.nlm.nih.gov/pubmed/10071710>]

35. The Department of Anesthesiology and Intensive Care, Helsingborg Hospital, Helsingborg, Sweden studied the release of melatonin in 8 intensive care patients and found: "Sleep disturbance is common in intensive care patients. Reasons for sleep deprivation appear to be multifactorial, including the underlying illness, an acute superimposed disturbance, medications, and the ICU environment itself. Melatonin levels in blood and urine were studied over 3 consecutive days in eight critically ill patients during deep sedation and mechanical ventilation. Sedation was assessed with the sedation-agitation (SAS) scale and bispectral index (BIS) monitor. The circadian rhythm of melatonin release was abolished in all but one patient, who recovered much more quickly than the others." [<http://www.ncbi.nlm.nih.gov/pubmed/15196098>]
36. Melatonin is produced by the pineal gland during theta and delta brainwave activity, which occurs during REM or deep sleep and also during meditation. In a study conducted by the School of Psychology, La Trobe University, Australia, researchers found: "Experienced meditators practising either TM-Sidhi or another internationally well known form of yoga showed significantly higher plasma melatonin levels in the period immediately following meditation compared with the same period at the same time on a control night. It is concluded that meditation, at least in the two forms studied here, can affect plasma melatonin levels." [<http://www.ncbi.nlm.nih.gov/pubmed/10876066>]
- Evidence of the Link Between Low Melatonin Levels and Reduced Immunity, Specifically on Production of IL-1 (Interleukin 1) and IL-2 (Interleukin 2)
  37. The Institute of Clinical Investigations, Faculty of Medicine, University of Zulia, Venezuela studied the effect of melatonin on IL-1 $\beta$  (interleukin 1 beta) and IL-2 (interleukin 2) production in mice and found: "The in vivo or in vitro treatment with MLT (melatonin) increased the levels of IL-2 (interleukin 2) and IL-1 beta in the absence or the presence of PHA, maintaining the increase in the concentration of IL-1 beta up to the ninth day of treatment. These results suggest that MLT (melatonin) acts directly on cell proliferation probably by binding to high affinity receptors located on spleen cells that stimulate the production of IL-2 and IL-1 beta giving rise to an increment of cell immunity." [<http://www.ncbi.nlm.nih.gov/pubmed/12703182>]
  38. The Institute of Clinical Investigations, Faculty of Medicine, University of Zulia, Venezuela further studied the effect of melatonin on the immune system in mice infected with VEE (Venezuelan equine encephalomyelitis) virus and found: "Levels of IFN- $\gamma$  (interferon-gamma) in the MLT (melatonin)-treated group were significantly increased when compared with the control non-infected group from day 1 to 6 post-infection. In infected mice treated with MLT, blood levels of IL-1 $\beta$  (interleukin 1 beta) were elevated almost 10-fold from day 1 to day 6 (post-infection) when compared to the control, the infected and the non-infected MLT-treated mice. A highly significant rise of TNF- $\alpha$  was found in infected mice treated with MLT (melatonin), from day 1 to 6 p.i. when compared to the other groups." [<http://trstmh.oxfordjournals.org/content/96/3/348.abstract>]
  39. The Medical College of Fudan University, China demonstrated injecting traumatized rats with melatonin was able to recover immune system function. "The present study was to evaluate the effect of melatonin (MT) and EA on the cytotoxic activity of natural killer (NK) cells, the dynamic changes of the induction of interleukin-2(IL-2) and the content of POMC-derived peptides, beta-endorphins (betaE) and ACTH in spleen lymphocytes and in plasma of traumatic rats. The results showed that intraperitoneal (i.p.) injection of MT (melatonin) was able to recover the lower levels of NK (natural killer) cell [immune system] activity and the induction of IL-2 (interleukin 2) production." [<http://www.ncbi.nlm.nih.gov/pubmed/12269723>]
  40. The Department of Medical Biochemistry and Molecular Biology, School of Medicine and Virgen Macarena Hospital, University of Seville, Spain demonstrated melatonin's role in the production of interleukin 2. "We investigated whether endogenous melatonin produced by Jurkat cells (T cells) was involved in the regulation of IL-2 (interleukin 2) production. When melatonin membrane and nuclear receptors were blocked using specific antagonists, luzindole and CGP 55644, respectively, we found that IL-2 production decreased, and this drop was reverted by exogenous melatonin. These findings indicate that endogenous melatonin synthesized by human T cells would contribute to regulation of its own interleukin 2 production, acting as an intracrine, autocrine, and/or paracrine substance." [<http://www.ncbi.nlm.nih.gov/pubmed/16021634>]
  41. A groundbreaking study conducted by the Shock and Trauma Research Laboratories, Department of Surgery, Michigan State University found melatonin significantly improved depressed immune system cell function in mice. "The results indicate that melatonin administration after trauma-hemorrhage significantly improved



the depressed immune functions, as evidenced by the restoration of Mphi IL-1 and IL-6 release, as well as significantly improved splenocyte IL-2 (interleukin 2) and IL-3 release and splenocyte proliferative capacity. This is the first study to show that melatonin, which is reported to be free of adverse side effects, can be considered a safe and effective therapeutic agent for restoring the depressed immunological function after soft-tissue trauma and hemorrhagic shock." [http://www.ncbi.nlm.nih.gov/pubmed/8661207]

42. In a study conducted by the Department of Molecular Pharmacology and Biologic Chemistry, Northwestern University Medical School, Chicago, researchers found: "Above the activation threshold of  $5 \times 10^{(-11)}$  M, melatonin was able to induce the cytotoxicity of human monocytes, the secretion of IL-1 (interleukin 1), and the production of reactive oxygen intermediates." [http://www.ncbi.nlm.nih.gov/pubmed/8077674]
43. The Division of Radiation Oncology, S. Gerardo Hospital, Monza, Italy conducted a study of 30 patients with gastrointestinal tract tumors to determine the effect of IL-2 (interleukin 2) therapy combined with melatonin. "The study included 30 patients with gastrointestinal tract tumors, who were randomized to undergo surgery alone, or surgery plus a preoperative biotherapy with high-dose IL-2 (18 million IU/day subcutaneously for 3 days) or low-dose IL-2 (6 million IU/day subcutaneously for 5 days) plus MLT (melatonin) (40 mg/day orally). Both IL-2 plus MLT (melatonin) were able to prevent surgery-induced lymphocytopenia. However, mean number of lymphocytes, T lymphocytes and T helper lymphocytes observed on day 1 of postoperative period was significantly higher in patients treated with IL-2 (interleukin 2) plus MLT (melatonin) than in those receiving IL-2 (interleukin 2) alone." [http://www.ncbi.nlm.nih.gov/pubmed/8553906]
44. The Division of Radiation Oncology, San Gerardo Hospital, Italy performed a clinical trial in locally advanced or metastatic patients with solid tumours to ascertain the effects of melatonin on IL-2 production therapy. "The study included 80 consecutive patients, who were randomised to be treated with IL-2 (interleukin 2) alone subcutaneously (3 million IU day<sup>-1</sup> at 8.00 p.m. 6 days a week for 4 weeks) or IL-2 plus MLT (melatonin) (40 mg day<sup>-1</sup> orally at 8.00 p.m. every day starting 7 days before IL-2). A complete response was obtained in 3/41 patients treated with IL-2 plus MLT and in none of the patients receiving IL-2 alone. A partial response was achieved in 8/41 patients treated with IL-2 plus MLT and in only 1/39 patients treated with IL-2 alone. Tumour objective regression rate was significantly higher in patients treated with IL-2 and MLT than in those receiving IL-2 alone (11/41 vs 1/39). The survival at 1 year was significantly higher in patients treated with IL-2 and MLT than in the IL-2 group (19/41 vs 6/39). Finally, the mean increase in lymphocyte and eosinophil number was significantly higher in the IL-2 plus MLT group than in patients treated with IL-2 alone; on the contrary, the mean increase in the specific marker of macrophage activation neopterin was significantly higher in patients treated with IL-2 alone." [http://www.ncbi.nlm.nih.gov/pubmed/8286206]
45. The Division of Radiation Oncology, San Gerardo Hospital, Italy performed a further study on AIDS patients to demonstrate the effects of melatonin on IL-2 (interleukin 2) immune performance and overall immune function. "A phase-II pilot clinical study was performed to evaluate the effects of low-dose subcutaneous IL-2 (interleukin 2) with the pineal hormone melatonin (MLT) in AIDS patients with CD4 counts below 200/mm<sup>3</sup>. The study included 11 patients. IL-2 (interleukin 2) was given subcutaneously at 3 million IU/ day in the evening for 6 days/week for 3 weeks. MLT (melatonin) was given orally at 40 mg/day in the evening every day, starting 7 days prior to IL-2. An increase in CD4 cell number greater than 30% occurred in 4/11 (36%) patients, and CD4 cell mean values observed during the study were significantly higher with respect to those found before. In addition, the treatment induced a significant increase in mean number of lymphocytes, eosinophils, T lymphocytes, NK cells, CD25- and DR-positive lymphocytes. Finally, CD4/CD8 mean ratio significantly increased during the study." [http://www.ncbi.nlm.nih.gov/pubmed/8844341]
46. The Department of Clinical Pathophysiology, University of Florence, Italy conducted a study to determine the effect of melatonin on immune system function in cancer patients. "There is growing evidence that the pineal gland has antineoplastic properties, which include the action of melatonin (MLT) on the immune system through the release of cytokines by activated T-cells and monocytes. The present study was carried out on 23 patients (15 males and 8 females, range 48-71 years), with advanced solid tumors, who received MLT (10 mg/day orally for a month) after conventional therapy. Blood was assayed for tumor necrosis factor alpha (TNF-alpha), Interleukin-2 (IL-2) and human interferon gamma (IFN-gamma). Circulating levels of TNF-alpha, IL-2 and IFN-gamma increased by 28%, 51% and 41% respectively after MLT (melatonin) administration. These findings are consistent with the hypothesis that MLT (melatonin) modulates immune functions in cancer patients by activating the cytokine system." [http://www.ncbi.nlm.nih.gov/pubmed/21597686]
47. In a study conducted by the Medical University Sofia, Bulgaria, significantly decreased melatonin levels were found in patients with the autoimmune disease Systemic Lupus Erythematosus (SLE) compared with healthy

controls. "SLE patients showed significantly lower daily melatonin levels in comparison to healthy women during the short photoperiod (17.75±7.13 pg/mL [16.05] vs. 21.63±6.60 pg/mL [20.10], p=0.012)." [http://www.balkanmedicaljournal.org/sayilar/39/buyuk/273-61.pdf]

➤ Evidence of the Link Between Low Melatonin Levels and Tumour Cell Growth

48. The First Affiliated Hospital of Xinxiang Medical University, China conducted a review of 8 randomized controlled studies to determine the effect of melatonin on tumour cell growth. "We performed a systematic review of randomized controlled trials (RCTs) of melatonin in 761 solid tumor cancer patients and observed its effect on tumor remission, 1-year survival, and side effects due to radiochemotherapy. The dosage of melatonin used in the 8 included RCTs was 20 mg orally, once a day. Melatonin significantly improved the complete and partial remission (16.5 vs. 32.6%; RR = 1.95, 95% CI, 1.49-2.54) as well as 1-year survival rate (28.4 vs. 52.2%; RR = 1.90; 95% CI, 1.28-2.83), and dramatically decreased radiochemotherapy-related side effects including thrombocytopenia (19.7 vs. 2.2%; RR = 0.13; 95% CI, 0.06-0.28), neurotoxicity (15.2 vs. 2.5%; RR = 0.19; 95% CI, 0.09-0.40), and fatigue (49.1 vs. 17.2%; RR = 0.37; 95% CI, 0.28-0.48). Melatonin as an adjuvant therapy for cancer led to substantial improvements in tumor remission, 1-year survival, and alleviation of radiochemotherapy-related side effects." [http://www.ncbi.nlm.nih.gov/pubmed/22271210]
49. The Laboratory of Experimental Neuroendocrinology/Oncology, Bassett Research Institute reports: "Over the past few years, we have shown that the surge of melatonin in the circulation during darkness represents a potent oncostatic signal to tissue-isolated rat hepatoma 7288CTC, which is an ER+ (estrogen positive) adenocarcinoma of the liver. This oncostatic effect occurs via a melatonin receptor-mediated suppression of tumor cAMP production that leads to a suppression of the tumor uptake of linoleic acid (LA), an essential fatty acid with substantial oncogenic properties. The ability of LA to promote cancer progression is accomplished by its intracellular metabolism to 13-hydroxyoctadecadienoic acid (13-HODE) which amplifies the activity of the epidermal growth factor receptor/mitogen-activated protein kinase pathway leading to cell proliferation. By blocking tumor LA uptake, melatonin effectively blocks the production of 13-HODE and thus, markedly attenuates (reduces) tumor growth. A similar effect of melatonin is observed in tissue-isolated, ER+ MCF-7 human breast cancer xenografts and nitrosomethylurea (NMU)-induced rat mammary cancers. When male rats bearing tissue-isolated hepatomas (liver cancers) are exposed either to constant bright light (300 lux) or dim light (0.25 lux) during the dark phase of a 12L:12D photoperiod, the latency to onset was significantly reduced while the growth of tumors was markedly increased over a 4 wk period as compared with control tumors in 12L:12D-exposed rats. In constant light- and dim light during darkness-exposed rats, melatonin levels were completely suppressed while tumor growth, LA uptake and 13-HODE production were markedly increased. Similar results were obtained in constant bright light-exposed female rats bearing tissue-isolated NMU-induced mammary cancers or MCF-7 human breast cancer xenografts. To date, these studies provide the most definitive experimental evidence that light exposure during darkness increases the risk of cancer progression via elimination of the nocturnal melatonin signal and its suppression of tumor LA (linoleic acid) uptake and metabolism to 13-HODE." [http://www.ncbi.nlm.nih.gov/pubmed/12163849]
50. In a study of mice conducted by The University of Seville School of Medicine and Virgen Macarena Hospital, Seville, Spain, researchers found: "Melatonin exhibits oncostatic properties, but the actual mechanism of action by which the indole (melatonin compound) reduces tumor cell activity is not clear. Telomerase is an enzyme responsible of telomere elongation and is activated in most human cancers. In the current in vivo study, eight nude mice received a MCF-7 [human breast cancer] xenograft and thereafter they were treated for 5 weeks with 0.1 mg/mL of melatonin in the drinking water. Melatonin treatment caused a significant reduction in the weight of tumors and reduced metastases when compared with the control group." [http://www.ncbi.nlm.nih.gov/pubmed/12932205]
51. The Canadian College of Naturopathic Medicine reviewed data from 21 clinical trials to determine the effect of melatonin on tumour cell growth and found: "The authors systematically reviewed the effects of MLT (melatonin) in conjunction with chemotherapy, radiotherapy, supportive care, and palliative care on 1-year survival, complete response, partial response, stable disease, and chemotherapy-associated toxicities. The authors included data from 21 clinical trials, all of which dealt with solid tumors. The pooled relative risk (RR) for 1-year mortality was 0.63 (95% confidence interval [CI] = 0.53-0.74; P < .001). Improved effect was found for complete response, partial response, and stable disease with RRs of 2.33 (95% CI = 1.29-4.20), 1.90 (1.43-2.51), and 1.51 (1.08-2.12), respectively. In trials combining MLT (melatonin) with chemotherapy, adjuvant MLT decreased 1-year mortality (RR = 0.60; 95% CI = 0.54-0.67) and improved outcomes of complete response, partial response, and stable disease; pooled RRs were 2.53 (1.36-4.71), 1.70 (1.37-2.12), and 1.15

(1.00-1.33), respectively. In these studies, MLT also significantly reduced asthenia, leucopenia, nausea and vomiting, hypotension, and thrombocytopenia." [<http://www.ncbi.nlm.nih.gov/pubmed/22019490>]

52. The Division of Radiation Oncology, S. Gerardo Hospital, Italy studied the effects of melatonin on patients with advanced stage cancer and found: "The aim of this study was to evaluate the effects of concomitant MLT (melatonin) administration on toxicity and efficacy of several chemotherapeutic combinations in advanced cancer patients with poor clinical status. The study included 250 metastatic solid tumour patients (lung cancer, 104; breast cancer, 77; gastrointestinal tract neoplasms, 42; head and neck cancers, 27), who were randomized to receive MLT (melatonin) (20 mg/day orally every day) plus chemotherapy, or chemotherapy alone. The 1-year survival rate and the objective tumour regression rate were significantly higher in patients concomitantly treated with MLT (melatonin) than in those who received chemotherapy (CT) alone (tumour response rate: 42/124 CT + MLT versus 19/126 CT only; 1-year survival: 63/124 CT + MLT versus 29/126 CT only)." [<http://www.ncbi.nlm.nih.gov/pubmed/10674014>]
  53. The Division of Radiation Oncology, S. Gerardo Hospital, Italy studied the effects of melatonin on patients with non-small lung cancer and found: "The present study was performed to assess the 5-year survival results in metastatic non-small cell lung cancer patients obtained with a chemotherapeutic regimen consisting of cisplatin and etoposide, with or without the concomitant administration of melatonin (20 mg/day orally in the evening). The study included 100 consecutive patients who were randomized to receive chemotherapy alone or chemotherapy and melatonin. Both the overall tumor regression rate and the 5-year survival results were significantly higher in patients concomitantly treated with melatonin. In particular, no patient treated with chemotherapy alone was alive after 2 years, whereas a 5-year survival was achieved in three of 49 (6%) patients treated with chemotherapy and melatonin." [<http://www.ncbi.nlm.nih.gov/pubmed/12823608>]
  54. The Division of Radiation Oncology, S. Gerardo Hospital, Italy studied the effects of melatonin on patients with metastatic breast cancer: "The study included 14 patients with metastasis who did not respond (n = 3) to therapy with TMX (tamoxifen) alone or progressed after initial stable disease (SD) (n = 11). MLT (melatonin) was given orally at 20 mg day<sup>-1</sup> in the evening, every day starting 7 days before TMX, which was given orally at 20 mg day<sup>-1</sup> at noon. A partial response was achieved in 4/14 (28.5%) patients (median duration 8 months). Mean serum levels of insulin-like growth factor 1 (IGF-1), which is a growth factor for breast cancer, significantly decreased on therapy, and this decline was significantly higher in responders than in patients with SD (stable disease) or progression." [<http://www.ncbi.nlm.nih.gov/pubmed/7710954>]
  55. The Laboratory of Molecular Biology, Anhui Medical University, China studied the effects of melatonin on patients with gastric cancer. "We investigated the effects of melatonin on cell proliferation, apoptosis (cell death), colony formation and cell migration in the gastric adenocarcinoma cell line, SGC7901, using MTT assay, Hoechst 33258 staining, flow cytometry, western blot, caspase-3 activity assay, soft agar colony formation assay, and scratch-wound assay. Our results showed that melatonin could inhibit cell proliferation, colony formation and migration efficiency, and it promoted apoptosis (programmed cell death) of SGC7901 cells. Our findings suggest that the anti-cancer effects of melatonin may be due to both inhibition of tumor cell proliferation and reduction of the metastatic potential of tumor cells." [<http://www.ncbi.nlm.nih.gov/pubmed/23477595>]
  56. The Department of Obstetrics and Gynecology, St Marianna University School of Medicine, Japan studied the effects of melatonin on patients with endometrial cancer. "The effect of melatonin on endometrial cancer cell growth was investigated using two cell lines, SNG-II and Ishikawa, which are different in their estrogen receptor status. Melatonin significantly inhibited Ishikawa cells, which are estrogen receptor-positive at all cell densities tested after 96 hr incubation. The greatest inhibition of Ishikawa cell growth was observed at 10<sup>(-9)</sup> M melatonin, compared with other supra (10<sup>(-6)</sup>, 10<sup>(-8)</sup> M) or subphysiological concentrations (10<sup>(-10)</sup>, 10<sup>(-12)</sup> M). This is the first study to demonstrate an anti-proliferative effect of physiological melatonin on endometrial cancer cells in vitro." [<http://www.ncbi.nlm.nih.gov/pubmed/10831158>]
- Evidence of the Link Between Low Levels of IL-2 (Interleukin 2) and Tumour Cell Growth
57. The Department of Medicine, University of Toronto, found mice deficient in IL-2 (interleukin 2) develop colon cancer spontaneously when exposed to ulcerative colitis, or irritable bowel syndrome. "Mice deficient in beta(2)-microglobulin and interleukin 2 (beta(2)m(null) x IL-2(null)) spontaneously develop colon cancer in the setting of chronic ulcerative colitis (UC)." [<http://www.ncbi.nlm.nih.gov/pubmed/11559569>]

58. In a study of 159 cancer patients, the Department of Internal Medicine, University of Cagliari, Italy found IL-2 (interleukin 2) deficiency was the primary cause of immune impairment linked to tumour cell growth. "Cancer sites were: larynx, 49; breast, 42; lung (NSC), 25; colorectal, 18; and gynecologic, 25. Our results provided evidence that the cancer patients exhibit a T cell functional immunodepression, which progresses during tumor growth, so that the localized disease shows a low-grade defect and advanced disease shows a high-grade defect. Our data also clearly suggested that the factor involved with a primary role in this functional immune impairment is the IL 2 (interleukin 2) deficiency." [<http://www.ncbi.nlm.nih.gov/pubmed/3263194>]
59. The Department of Surgery, Roger Williams Medical Center, Providence, Rhode Island studied 66 patients with high stage head and neck cancer, where the immune system is known to be frequently depressed. "LAK cell function at low-dose IL-2 was depressed in 45% of the patients (9 of 20) and was restored by increased IL-2 (1,000 U/mL) or a combination of IL-2 and INF-alpha. Half of the patients had depressed expression of the low-affinity IL-2 (interleukin 2) receptor (CD25)." [<http://www.ncbi.nlm.nih.gov/pubmed/8214299>]
60. The Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health finds: "CD4+CD25+ T regulatory (Treg) cells control immunologic tolerance to self-antigens and play a role in suppressing antitumor immune responses, but the mechanism of suppression in vivo remains uncertain. Recently, signaling through the high-affinity interleukin-2 (IL-2) receptor has been shown to be critical for Treg cell differentiation and survival in vivo. Mice deficient in IL-2 (interleukin 2) or its receptor (CD25 or CD122) or deficient in downstream signaling molecules, including JAK-3 and STAT-5, do not develop a stable population of Treg cells and subsequently acquire lymphoproliferative disease and autoimmunity. In vitro, IL-2 (interleukin 2) is required to expand Treg cells and to induce their suppressive characteristics. Conversely, IL-2-based regimens can activate cellular antitumor immunity and are the mainstay of immunotherapies directed against melanoma and kidney cancers." [<http://www.ncbi.nlm.nih.gov/pubmed/15725955>]
61. The Surgery Branch, Biostatistics and Data Management Section, Department of Pathology, National Cancer Institute conducted a study of 156 metastatic renal cell cancer patients with both high dose and low dose IL-2 (interleukin 2). "There was a higher response proportion with HD (high dose) IV IL-2 (21%) versus LD (low dose) IV IL-2 (13%; P =.048) but no overall survival difference. Major tumor regressions, as well as complete responses, were seen with all regimens tested." [<http://www.ncbi.nlm.nih.gov/pubmed/12915604>]
62. The Division of Cancer Treatment, National Cancer Institute states: "We have administered 1039 courses of high-dose interleukin-2 (IL-2) to 652 cancer patients. Five hundred ninety-six patients had metastatic cancer that either had failed standard effective therapies or had disease for which no standard effective therapy existed, and 56 patients were treated in the absence of evaluable disease in the adjuvant setting. Initial results with the treatment of high-dose IL-2 (interleukin 2) alone or in conjunction with LAK cells have indicated that objective regressions of cancer can be achieved in 20% to 35% of patients with selected advanced metastatic cancers. Although most responses have been seen in patients with metastatic renal cell cancer, melanoma, colorectal cancer, and non-Hodgkin's lymphoma, many histologic types of cancer have not been treated in significant numbers. These regressions can be durable; of 18 patients achieving a complete response, ten have not experienced recurrence at intervals from 18 to 52 months. These studies demonstrate that a purely immunologic manipulation can mediate the regression of advanced cancers in selected patients and may provide a base for the development of practical, effective biologic treatments for some cancer patients." [<http://www.ncbi.nlm.nih.gov/pubmed/2679456>]
63. In a study of 181 patients with metastatic renal cell cancer, the Department of Oncology Aarhus University Hospital and Institute of Medical Microbiology and Immunology, Denmark studied the effects IL-2 on tumour cell growth. "120 Danish patients, 41 UK patients and 20 Swedish patients were treated with low or intermediate dose IL-2 (interleukin 2) based immunotherapy in an outpatient setting. In the Danish patients, an estimated 5-year survival rate of 16% was observed. From the blood and tumor analysis, an understanding emerged that IL-2 based immunotherapy is a "targeted therapy" requiring intratumoral immune cells (CD4+, CD8+, CD56+, CD57+ T- and NK cells) for treatment effect. In contrast, monocytes and neutrophils were harmful for the outcome of IL-2 based immunotherapy." [<http://www.ncbi.nlm.nih.gov/pubmed/18208677>]
64. The Department of Surgery, Tohoku University School of Medicine, Japan, discovered interferon gamma (IFN $\gamma$ ) to be the crucial link between interleukin 2 (IL-2) stimulating the production of lymphokine activated killer (LAK) cells; key cancer-fighting immune system cells. "The generation of lymphokine activated killer (LAK) cells by recombinant IL2 (interleukin 2) (rIL2) in collaboration with interferon $\gamma$  (IFN $\gamma$ ) was examined in peripheral blood mononuclear cells (PBMC) from patients with malignant tumors of the digestive organs and breast cancer. LAK cytotoxicity could be induced by rIL2 at 10 units/ml in 10 of 12 patients and 20 of 37 using

fresh autologous tumor cells and PK-1, an established solid tumor cell line as a target, respectively. Among 34 patients [given rIL-2], in which titers of IFN $\gamma$  produced were assayed, 12 showed no IFN $\gamma$  production. All of these 12 patients had no or extremely low LAK activity, suggesting the correlation of LAK generation with the production of IFN $\gamma$  in response to rIL2. These results indicate that [immune] LAK (lymphokine activated killer cell) induction by rIL2 (recombinant interleukin 2) in cancer patients involves the production of IFN $\gamma$  and its interaction with rIL2." [<http://link.springer.com/article/10.1007%2FBF00199859>]

65. The Department of Haematology, University of Leipzig, Germany found natural Killer (NK) cells "activated" by interleukin 2 to produce four known immune system responses: [1. lymphokine activated killer (LAK) cell generation, 2. interferon-gamma (IFN $\gamma$ ), 3. IL-2 receptor, 4. CD69] increased the ability of NK cells to bind the cancer-killing chemical "perforin" to the tumour cell surface, resulting in a significant increase in tumour-cell death. "Natural killer (NK) cells can lyse (breakdown) a variety of different tumour cells by exocytosis of perforin, subsequent binding of perforin to the target cell membrane and formation of lytic pores. Some tumour cells, however, are resistant to cellular cytotoxicity. Using the NK-resistant tumour cell lines ML-2, MONOMAC-1, RPMI and L540Cy, we demonstrated that activation of NK cells with interleukin 2 and IL-12 resulted in significant lysis of these tumour targets." [<http://www.ncbi.nlm.nih.gov/pubmed/11552995>]
66. The University of Pittsburgh Cancer Institute, University of Pittsburgh found mice injected with interleukin 2 (IL-2) and natural killer cells "activated" by interleukin 2 caused a 65-90% destruction of well-established lung metastases. "We have shown previously that i.v. injection of interleukin-2-(IL-2) activated natural killer (A-NK) cells together with IL-2 leads to a substantial localization of the A-NK cells into most, but not all, well-established B16 lung metastases in C57BL/6 mice within 12-24 hr. We demonstrate that the morphology of the lung metastases, (loose or more compact in appearance), and their location in the lungs (on the surface or deep in the lung parenchyma) are closely tied to the infiltration-permissiveness of the metastases as well as their sensitivity to treatment with A-NK cells. Although more than 1100 A-NK cells/mm<sup>2</sup> were found in deep metastases with a "loose" morphology (D-L), only 534, 90 and 89 cells/mm<sup>2</sup> were found in surface-loose (S-L), surface-compact (S-C) and deep-compact (D-C) metastases, respectively. The best infiltrated metastases responded best to the A-NK cell therapy. Thus, metastases of the D-L phenotype became reduced by 65-90% after treatment with 2 x 10<sup>6</sup> A-NK cells and IL-2 (120000 IU Peg-IL-2 every 12 hr for 3 days) compared to similar lesions in animals treated with PEG-IL-2 alone. In contrast, poorly infiltrated metastases, that is lesions of the compact phenotype (D-C and S-C) as well as loose metastases on the lung surface (S-L), did not react significantly to this treatment. We conclude that adoptively transferred [IL-2] A-NK cells are able to eliminate even well-established metastases." [<http://www.ncbi.nlm.nih.gov/pubmed/12712443>]

➤ Evidence of the Link Between Low Levels of IL-2 (Interleukin 2) and Increased Microbial Infection

67. In a study conducted by the Department of Epidemiology, University of Alabama at Birmingham, researchers found interleukin 2 levels were significantly lower in subjects with Chlamydia infection. "We examined the endocervical production of two T(H)1-associated cytokines, i.e. interleukin (IL)-2 and IL-12, in relation to C. trachomatis infection in adolescents. At a randomly selected visit for 396 females, median endocervical IL-2 (interleukin 2) levels were significantly lower (190 versus 283 pg/ml, P = 0.02) and median IL-12 levels significantly higher (307 versus 132 pg/ml, P < 0.001) in subjects testing positive versus negative for C. trachomatis [Chlamydia infection]." [<http://www.ncbi.nlm.nih.gov/pubmed/16297168>]
68. The Department of Clinical Medicine, University of Oxford, United Kingdom found interleukin 2 (IL-2) levels were significantly lower in those with chronic hepatitis C infection. "We analyzed cytokine secretion patterns in chronically infected patients and compared them with those with resolved infection. In the spontaneous resolver group, strong IL-2 secretion in relation to IFN-gamma secretion was observed. However, in the persistently infected group, a consistent and significant loss of IL-2 (interleukin 2)-secreting cells, compared with IFN-gamma-secreting cells, was identified. In vitro addition of IL-2 had a substantial effect in restoring CD4+ T cell activity. In conclusion, failure of IL-2 (interleukin 2) secretion, as opposed to physical deletion or complete functional unresponsiveness, appears to be an important determinant of the status of CD4+ T cell populations in chronic HCV infection." [<http://www.ncbi.nlm.nih.gov/pubmed/15841456>]
69. In a study conducted by the Department of Infectious Disease Immunology, Statens Serum Institut, Denmark, researchers found an almost complete disappearance of interleukin 2-producing CD4 T cells in the presence of tuberculosis infection. "We show in this article that although bacille Calmette-Guérin (vaccine) controlled M. tuberculosis growth for 7 wk of infection, the protection was gradually lost as the infection entered the chronic phase. The regrowth of M. tuberculosis coincided with an almost complete disappearance of IL-2 (interleukin 2)-producing CD4 T cells." [<http://www.ncbi.nlm.nih.gov/pubmed/23677471>]

70. In a study conducted by the Beijing Hospital, researchers found patients with acute stage pneumonia [caused by viral-bacterial infection], was associated with significantly reduced interleukin 2 (IL-2) production. "The capacity of IL-2 production of peripheral blood lymphocyte (PBL), were determined in 54 patients with pneumonia in acute stage and 33 cases in convalescent stage. 20 elderly COPD (chronic obstructive lung disease) in remission patients and 59 healthy control (32 aged 20-55 and 27 over 60) were determined also. It was shown that the capacity of IL-2 (interleukin 2) production of the patients with pneumonia in acute stage were markedly lower than healthy control." [<http://www.ncbi.nlm.nih.gov/pubmed/1394576>]
71. In a study conducted by the AIDS Clinical Center, International Medical Center of Japan, Toyko, researchers found interleukin 2 (IL-2) production was significantly lower in patients with the human immunodeficiency virus (HIV) compared to healthy controls, and became increasingly lower in patients who expressed higher viral loads. "A total of 48 HIV-1-infected (HIV+) and 16 HIV-1-uninfected (HIV-) individuals were studied. The percentages of CD4+ CD8- T cells producing interleukin-2 (IL-2), interferon-gamma, interleukin-4 (IL-4), or interleukin-5 (IL-5) in HIV+ and HIV- subjects were 23.6% versus 34.9%, 13.7% versus 13.2%, 1.3% versus 1.0%, and 1.2% versus 0.9%, respectively. The population of IL-2 (interleukin 2)-producing cells decreased proportionately with reductions in CD4 counts (< 200/mm<sup>3</sup>, 200-500/mm<sup>3</sup>, and > 500/mm<sup>3</sup> to 18.0%, 23.5%, and 30.5%, P < 0.05, respectively). There was an inverse correlation between the percentage of IL-2 (interleukin 2)-producing cells and plasma viral load." [<http://www.ncbi.nlm.nih.gov/pubmed/10564559>]
72. The National Institute of Allergy and Infectious Diseases, National Institutes of Health, studied the effect of interleukin 2 (IL-2) on the human immunodeficiency virus (HIV) and found: "The size of the pool of resting [immune system] CD4+ T cells containing replication-competent HIV in the blood of patients receiving intermittent interleukin (IL)-2 plus highly active anti-retroviral therapy (HAART) was significantly lower than that of patients receiving HAART alone. Virus could not be isolated from the peripheral blood CD4+ T cells in three patients receiving IL-2 plus HAART, despite the fact that large numbers of resting CD4+ T cells were cultured. These results indicate that the intermittent administration of IL-2 (interleukin 2) with continuous HAART (anti-retroviral therapy) may lead to a substantial reduction in the pool of resting CD4+ T cells that contain replication-competent HIV." [<http://www.ncbi.nlm.nih.gov/pubmed/10371503>]
73. In a study conducted by the Department of Laboratory Medicine and Pathology, University of Minnesota Medical Center, Center for Immunology, Minneapolis, researchers found mice treated with interleukin 2 (IL-2) had greater protection from microbial infection. "IL-2 complexes have substantial effects on the cellular immune system, and this approach is being explored for therapeutic application in infection and cancer. In this study, we report that naive mice treated with a short course of IL-2 complexes show enhanced protection from newly encountered bacterial and viral infections." [<http://www.ncbi.nlm.nih.gov/pubmed/21037095>]
74. The Molecular Immunogenetics and Vaccine Research Section, National Cancer Institute studied the levels of interleukin 2 (IL-2) in 140 women exposed to the human papillomavirus (HPV). "Human papillomavirus (HPV) is believed to be the major cause of cervical cancer. To investigate whether a cellular immune response, especially a T helper type 1 response, is related to the natural defense against HPV-related cervical lesions, the interleukin 2 response of peripheral blood lymphocytes in vitro to overlapping peptides from HPV-16 E6 and E7 oncoproteins was compared with the degree of cervical cytological abnormality among 140 women in a cross-sectional study. We compared 66 women diagnosed with low-grade squamous intraepithelial lesions (LSIL), 21 with high-grade squamous intraepithelial lesions (HSIL), and 28 with invasive cervical cancer with 25 women who were cytologically normal but previously HPV-16 (human papillomavirus) DNA positive. The fraction showing strong interleukin 2 production against HPV-16 peptides was greatest among cytologically normal women (35%) and declined with increasing disease severity [LSIL] (20%), HSIL, (17%), and cancer patients (7%). Our finding suggests that a T helper lymphocyte type 1 (interleukin 2) response to HPV (human papillomavirus) antigens is associated with disease status." [<http://www.ncbi.nlm.nih.gov/pubmed/8752165>]
75. The Department of Microbiology and Immunology, Loyola University of Chicago studied the anti-microbial properties of interleukin 2 on the common fungus *Candida albicans*. "Murine splenocytes, Percoll-enriched low-density lymphocytes, and interleukin-2 (IL-2)-activated lymphocytes were assessed for the capacity to limit the growth of the hyphal form of *Candida albicans*. No fungal-growth-inhibitory activity was exhibited for *C. albicans* by either splenocytes or Percoll-enriched lymphocytes. However, when cultured for several days with IL-2 (interleukin 2), splenocytes acquired the capacity to inhibit the growth of the fungus. The antifungal activity of the IL-2-activated lymphocytes was exhibited against a number of clinical isolates of *C. albicans* and related fungal species. IL-2-activated human peripheral blood lymphocytes also acquired the capacity to inhibit the growth of *C. albicans*." [<http://www.ncbi.nlm.nih.gov/pubmed/1541559>]

# The 2<sup>nd</sup> Phase of Cancer

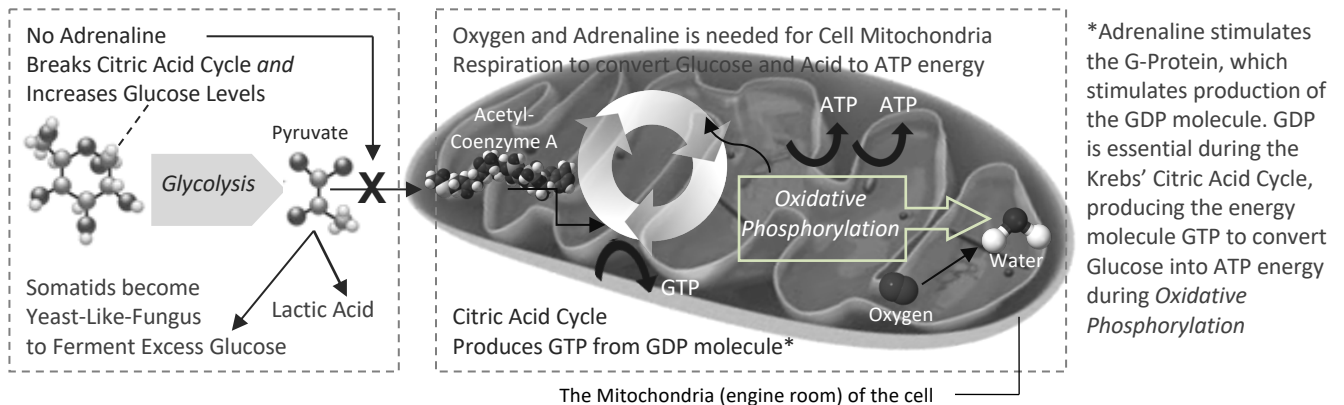


Stress Depletes Adrenaline Breaking the Cell's (Krebs) Citric Acid Cycle, Causing the Cell to Ferment Rising Glucose Levels

Phase

2

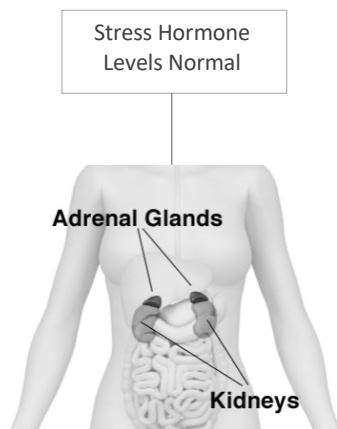
During phase 2, elevated stress hormone cortisol levels deplete all-important adrenaline (epinephrine) levels. There are limited reserves of adrenaline in the body and when an individual is under constant psycho-emotional stress these reserves are depleted quickly. While insulin is used to transport glucose into cells, it is adrenaline which is critical for cell respiration and for converting this glucose in the cell into ATP energy for the body and for healthy cell division [which occurs via the metabolic pathway known as Oxidative Phosphorylation and via the Krebs' Citric Acid Cycle of the mitochondria of the cell]. Without adrenaline to stimulate the G-Protein to stimulate production of the GDP molecule [which is essential for mitochondrial cell respiration and glucose conversion] the cell's Krebs' Citric Acid Cycle and Oxidative Phosphorylation metabolic pathway is broken and the cell is forced to ferment glucose instead as a means to obtain [smaller amounts of] ATP energy [via the process known as Glycolysis], which creates lactic acid in the cell and a low pH environment.



## The Theory

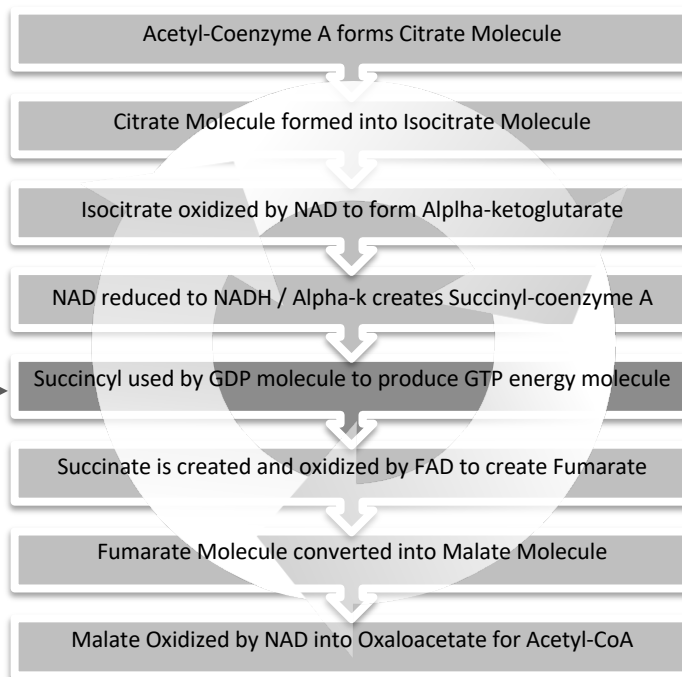
In 1931 Otto Warburg was awarded the Nobel Prize for Physiology in discovering the mechanism for mitochondrial cell respiration. As professor and director of the Kaiser Wilhelm Institute for Biology in Germany, he is most famous for his discoveries on cells mutating into cancer cells. This he discovered occurred due to loss of respiration within the cell's mitochondria, which subsequently resulted in the normal cell fermenting glucose as a secondary means to obtain energy for the body and cell [through the process known as Glycolysis]. This process of fermenting glucose occurs in the cytosol (or intracellular fluid) of the cell, causing a discharge of lactic acid. The discharge of lactic acid within the cell creates a low pH (or highly acidic) environment. Otto Warburg postulated the cause of the loss of cell respiration was—sounding most logical—a depletion of oxygen in the cell. And while this may play a small role, it is in fact the depletion of adrenaline that disrupts cell respiration above all. When an individual is under prolonged chronic psycho-emotional stress, adrenaline levels initially spike; yet over months and years of perpetual stress the adrenal glands suffer adrenal fatigue and in a number of cases the chronic debilitating condition known as adrenal insufficiency develops. In either case, adrenaline production is severely limited. This is especially important, as it is the job of adrenaline to initiate within cells the conversion of glucose into ATP energy for general bodily use and to provide energy for mitochondrial cell respiration. This is accomplished through adrenaline stimulating the G-Protein which subsequently stimulates production of the GDP molecule within cells. The Krebs' Citric Acid Cycle [which is akin to a large processing factory inside the mitochondria of the cell] uses the GDP molecule to produce the energy molecule GTP. The GTP molecule is used [together with oxygen] to convert glucose into ATP energy through the metabolic pathway known as Oxidative Phosphorylation. In cancer patients, the Krebs' Citric Acid Cycle [which is essential for optimal Oxidative Phosphorylation] comes to a halt without the all-important GDP molecule stimulated by adrenaline to keep the glucose-ATP-processing factory running, causing a build-up of glucose in the cell.

**Krebs' Citric Acid Cycle of the Cancer-Free Individual**



Adrenaline Levels Normal

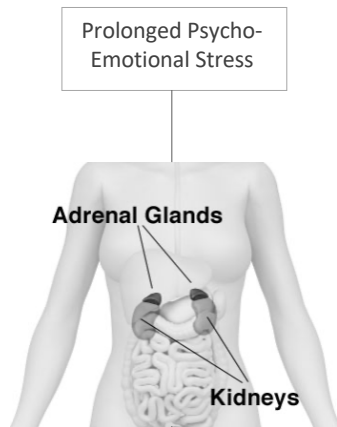
Adrenaline Stimulates G-Protein to Stimulate Production of GDP molecules within cells



ATP energy is created from GTP energy molecules, NADH and Succinate within the metabolic pathway known as *Oxidative Phosphorylation*

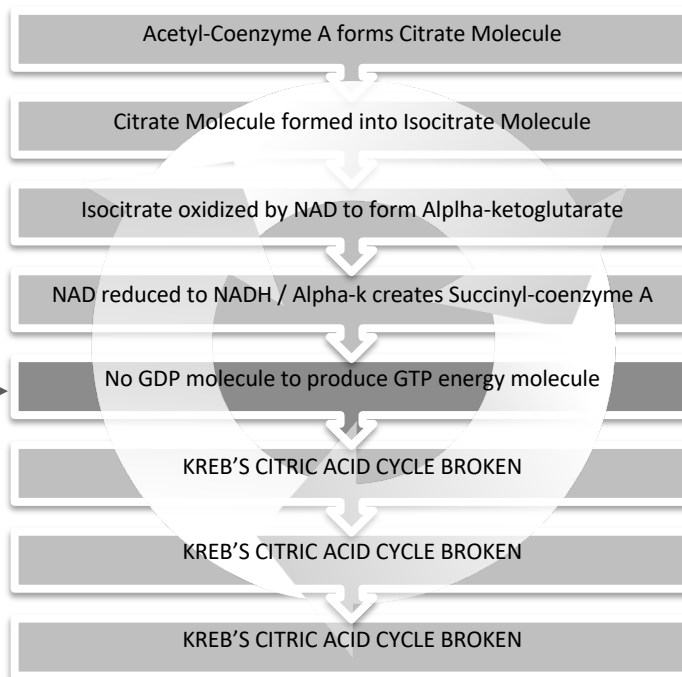
**Glucose is converted by Krebs' Citric Acid Cycle into ATP energy for the Cell and the Body**

**Krebs' Citric Acid Cycle of the Individual with Cancer**



Adrenaline Levels Depleted

Adrenaline unable to stimulate G-Protein to Stimulate Production of GDP molecules within cells



ATP energy unable to be created via Krebs' Citric Acid Cycle for *Oxidative Phosphorylation* due to absent GTP energy molecules, NADH and Succinate

**Krebs' Citric Acid Cycle unable to convert Glucose into ATP energy; the Cell Ferments Glucose Instead**



Otto Warburg states: "Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar (glucose). All normal body cells meet their energy needs by respiration of oxygen, whereas cancer cells meet their energy needs in great part by fermentation. All normal body cells are thus obligate aerobes [that grow only in the presence of oxygen], whereas all cancer cells are partial anaerobes [that don't need oxygen to grow]. From the standpoint of the physics and chemistry of life this difference between normal and cancer cells is so great that one can scarcely picture a greater difference. Oxygen gas, the donor of energy in plants and animals is dethroned in the cancer cells and replaced by an energy yielding reaction of the lowest living [microbial] forms, namely, a fermentation of glucose.

Cancer cells originate from normal body cells in two phases. The first phase is the irreversible injuring of [cell] respiration. The irreversible injuring of respiration is followed, as the second phase of cancer formation, by a long struggle for existence by the injured cells to maintain their structure, in which a part of the cells [the mitochondria] perish from lack of energy, while another part succeed in replacing the irretrievably lost respiration energy by fermentation energy.

Since the respiration of all cancer cells is damaged, our first question is, How can the respiration of body cells be injured? One method for the destruction of the respiration of body cells is removal of oxygen. If, for example, embryonal tissue is exposed to an oxygen deficiency for some hours and then is placed in oxygen again, 50 percent or more of the respiration is usually destroyed. The cause of this destruction of respiration is lack of [GTP and ATP] energy. As a matter of fact, the cells need their respiratory energy to preserve their structure, and if respiration is inhibited, both [mitochondrial] structure and [cell] respiration disappear. Another method for destroying [cell] respiration is to use respiratory poisons. From the standpoint of energy, this method comes to the same result as the first method. No matter whether oxygen is withdrawn from the cell or whether the oxygen is prevented from reacting [in the cell] by a poison, the result is the same in both cases – namely, impairment of respiration from lack of [GTP and ATP] energy.

When the respiration of body cells has been irreversibly damaged, cancer cells by no means immediately result. For cancer formation there is necessary not only an irreversible damaging of the respiration but also an increase in the fermentation. The driving force of the increase of fermentation, however, is the [GTP and ATP] energy deficiency under which the cells operate after destruction of their respiration, which forces the cells to replace the irretrievably lost respiration energy in some way. They are able to do this by a selective process that makes use of the fermentation of the normal body cells. The more weakly fermenting body cells perish, but the more strongly fermenting ones remain alive, and this selective process continues until the respiratory failure is compensated for energetically by the increase in fermentation. Only then has a cancer cell resulted from the normal body cell. Now we understand why the increase in fermentation takes such a long time and why it is possible only with the help of many cell divisions. Since the increase in fermentation in the development of cancer cells takes place gradually, there must be a transitional phase between normal body cells and fully formed cancer cells. Thus, for example, when fermentation has become so great that dedifferentiation has commenced, but not so great that the respiratory defect has been fully compensated for energetically by fermentation, we may have cells which indeed look like cancer cells but are still energetically insufficient. Such cells, which are clinically not cancer cells, have lately been found, not only in the prostate, but also in the lungs, kidney, and stomach of elderly persons. Such cells have been referred to as "sleeping cancer cells".

Figure 4 shows that the pathways of respiration and fermentation are common as far as pyruvic acid. Then the pathways diverge. The end products of fermentation are reached by one single reaction, the reduction of pyruvic acid by dihydro-

nicotinamide to lactic acid. On the other hand, the end products of the oxidation of pyruvic acid, H<sub>2</sub>O and CO<sub>2</sub>, are only reached after many additional reactions."

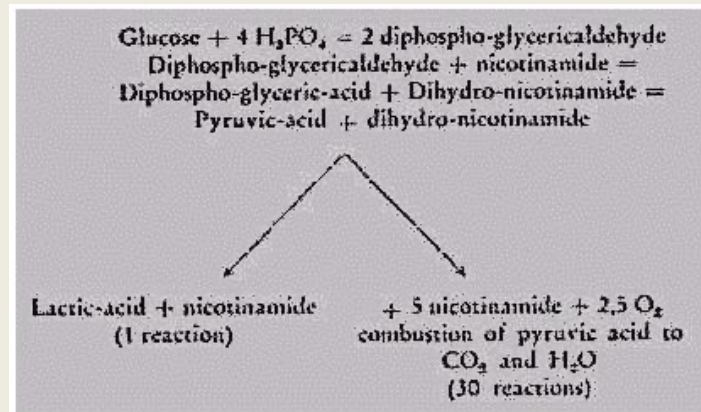


Figure 4



[Otto Warburg]

Dr Waltraut Fryda was a senior physician at the world-famous Issels' Ringberg Klinik in Germany. She wrote the book *Diagnosis: Cancer*, underscoring adrenaline depletion as a central causal component of cancer that destabilized the homeostasis of the body's correct tissue pH balance. Dr Fryda used adrenaline and the administration of the positive form of lactic acid [dextrorotatory lactic acid] to normalize the body's correct [acid-alkaline] pH balance and to restore health to many patients. In the excerpt from her book below she describes this mechanism.

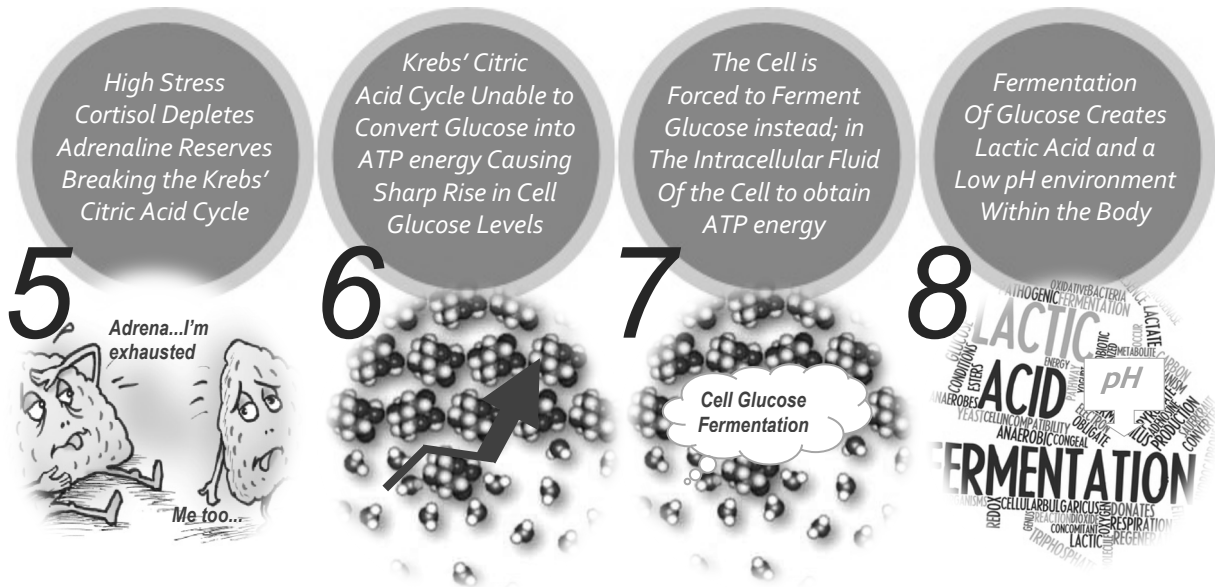
Dr Waltraut Fryda: "A cancer patient always suffers from over-acidification of the tissues. In order to deprive the tumour of a favourable environment, the tissue-pH value must be changed from acid to alkaline. This is easier said than done because all alkaline-forming nutrition loses its intended effect soon after entering the bloodstream, as it is used up in the blood for buffering, before it can reach the tissue. The [human bodily] organism always endeavours via appropriate regulating mechanisms to maintain the blood-pH value at around 7.4, which is absolutely essential for the stability of hormones, in particular adrenaline. A brief recapitulation of the law of reversed proportionality of pH value changes in blood and tissue: if the blood-pH value drops, the tissue-pH value rises (and vice versa). This gives us a kind of lever: it should be possible to indirectly raise an unhealthy acid-tissue-pH value by lowering the slightly alkaline blood-pH value.

Over-acidification of tissue is prevented in a healthy [human] organism by the dextrorotatory lactic acid that is constantly produced by movement and suitable nutrition. This, therefore, indicates that an input of optically dextrorotatory lactic acid is needed. This may seem like a contradiction to the layman, in that tissue is to be de-acidified by administering an acid. The paradox disappears, however, if

all interrelations are kept in mind. Acidification of the blood by means of dextrorotatory lactic acid [commercially available as Pleo Sanuvis®] lowers the blood-pH value until it and the tissue-pH value reach the same level. This takes precisely five weeks in cancer patients who are administered an appropriate dose of dextrorotatory lactic acid [thirty drops, three times daily]. This has been confirmed time and again by my own measurements over many years of the blood-pH value. During the period from the first until approximately the fourth day in week 6, the acid substances will be discharged from the tissue into the blood, the pH value of which drops for a short time to very low values. The excretion of the pathological substances of the tissue via blood, liver, kidneys, and skin during this period is apparent from an entirely pungent and acid smell. I am as yet unable to explain the reasons for the period of five weeks. However, the same physical and psychological symptoms occur after this [five week period]. Feeling generally unwell, the patient is irritable, aggressive, and depressed at the same time. At the height of this "changeover reaction", usually lasting for three days, the pH value of tissue and blood reach the same level.

The continued supply of dextrorotatory lactic acid (Pleo Sanuvis®) finally ensures an unproblematic and physiological restitution and maintenance of a blood-pH value of 7.4 and a tissue -pH value above that figure. This will remove a critical precondition for continued growth of a tumour in a cancer patient, namely the acid environment. Kidneys and liver are now capable of carrying out their full detoxification functions, thereby, laying the foundations for a safe removal of subsequently occurring disintegration products of a malignant tumour. Finally, dextrorotatory lactic acid also causes the biological neutralization of the toxic, levorotatory lactic acid of the tumour into a non-toxic, racemic form. This is of utmost importance, as it removes the stimulus for an increase in the cell division rate. Normalising the acid-alkali balance also stimulates adrenaline production and improves its effectiveness, an equally important precondition for a healthy [aerobic cell] metabolism. The therapy here introduced offers relatively great advantages to patients, because, the "changeover" reaction over three days excepted, they are not subjected to any stress. It is neither painful nor does it cause vomiting, loss of appetite, bleeding of the bladder, or other similar side effects that are well-known from aggressive therapies." [Note: Dextrorotatory lactic acid is a main ingredient in whey (the liquid component of cottage cheese) that is combined with flaxseed oil to form the Johanna Budwig Cancer Diet.]

Within the 2<sup>nd</sup> Phase of Cancer the following sequence of events can be observed in the cancer patient:



## The Evidence

The evidence for Phase 2 of Cancer can be broken down into the following components: a) the link between high stress hormone cortisol levels and depleted adrenaline (epinephrine) levels, b) the link between depleted adrenaline (epinephrine) levels and reduced respiration within the cell mitochondria, specifically relating to the Krebs' Citric Acid Cycle and Oxidative Phosphorylation, c) the link between reduced respiration within the cell mitochondria and increased cell glucose fermentation [via the process known as glycolysis], d) the link between glucose fermentation, tumor growth and increased cell lactic acid production, e) the link between increased cell lactic acid production and low pH levels in the cell and body, f) the link between cancer, tumor growth and depleted adrenaline reserves.

- Evidence of the Link Between High Stress Hormone Cortisol Levels and Depleted Adrenaline (Epinephrine) Levels
76. In a study conducted by the Department of Psychology, University of Virginia, researchers found adrenaline levels were depleted significantly after 27 days of prolonged inescapable shock. "Two experiments examined sympathetic-adrenal medullary responses of laboratory rats after exposure to a brief period of stressful stimulation daily for 26 consecutive days. In the first experiment, rats were exposed to restraint stress for 30 minutes per day and in the second experiment, rats were exposed to inescapable footshock for 10 minutes per day. In both experiments, chronically stressed rats gained less weight than controls. Basal plasma levels of norepinephrine (NE) and epinephrine (EPI) were similar in control and chronically stressed rats. However, there was a substantial attenuation (reduction) of the plasma [norepinephrine /epinephrine] catecholamine response to the 27th episode of restraint or footshock compared to acutely stressed controls. These findings indicate that sympathetic-adrenal medullary responses are dampened considerably in animals exposed to a highly predictable regimen of chronic intermittent stress." [<http://www.ncbi.nlm.nih.gov/pubmed/2756012>]
  77. In a study conducted by Keigo Nakagawa of the Department of Internal Medicine, Chuden Hospital, Japan, researchers found adrenaline levels depleted significantly in the adrenal glands after exposure to chronic stress. "When rats were exposed to immobilized cold stress, adrenaline (epinephrine) content in the adrenal gland as well as noradrenaline content in the brain stem were reduced drastically. Oral administrations of taurine [an enzyme found in bile that reduces blood pressure] (4-7 g/kg/day, for 3 days) prevented the stress-induced decline of adrenaline in the adrenal gland. In hypophysectomized rats [where the pituitary gland has been removed], the stress also induced a significant fall in adrenaline (epinephrine) content of the adrenal gland." [<http://www.ncbi.nlm.nih.gov/pubmed/6814>]
  78. In a study conducted by Juan M Saavedra of the National Institute of Mental Health, National Institutes of Health, a significant reduction in adrenaline levels were found in rats exposed to chronic stress conditions. "Catecholamines [adrenaline, noradrenaline and dopamine] have been measured in specific areas of the rat brain stem after acute immobilization stress. Adrenaline levels were significantly decreased after 240 min of immobilization [acute stress] in all areas studied: A1 area, nucleus commissuralis (NCO), A2 area, anterior part of the nucleus tractus solitarii (NTS), and the locus coeruleus. Noradrenaline concentrations in stressed rats were significantly reduced only in the NTS area." [<http://www.ncbi.nlm.nih.gov/pubmed/761066>]
  79. In a study conducted by the Department of Zoology, University of Calcutta, India, researchers found turtles exposed to dehydration stress had severely depleted adrenaline (epinephrine) levels. "Adult soft-shelled turtles were exposed to hyperosmotic and dehydration stresses. Dehydration [stress] for 7 days brought about depletion of serotonin and epinephrine (adrenaline) levels and elevation of norepinephrine (noradrenaline) level." [<http://www.ncbi.nlm.nih.gov/pubmed/1722440>]
  80. In a landmark study conducted by the Memorial Research Center and Hospital, University of Tennessee and the Department of Surgery, Medical College of Virginia, researchers followed 14 severe burn patients under chronic stress conditions who all subsequently died and found 71.5% had severely depleted adrenaline levels at the time of death. "The normal human adrenal contains 412 to 633 µg of adrenaline and 37 to 123 µg of noradrenaline. Adrenaline (epinephrine) is the principal hormone of the adrenal medulla and is released in increased amounts under various stressful situations, i.e., thermal burns, muscular exercise, centrifugation, and trauma. Normal young adult males excrete approximately 10 to 25 µg of adrenaline and 25 to 45 µg of noradrenaline per 24 hours. It is further known that the adrenal gland normally synthesizes adrenaline with such rapidity that only under unusual circumstances can the adrenal medulla be depleted of its adrenaline supply. It has been shown that most patients who survive severe thermal burns excrete daily large amounts of adrenaline and noradrenaline, and that this elevated rate of excretion continues for weeks without any recognizable failure in the adrenal glands ability to produce adrenaline. However, of the burned patients

who died, approximately two-thirds showed a markedly depressed adrenaline output at the time of death. The experiments herein described attempt to correlate this low adrenaline output with a low adrenaline content of the adrenal gland and further, to evaluate this finding in terms of an acute adrenal medullary insufficiency. A total of 14 severely burned patients was followed, all of whom died. In each patient, the daily 24-hour urinary output of adrenaline and noradrenaline was determined and at death, correlated to the adrenaline content of the adrenal gland. 71.5 per cent of all the burned patients, showed at the time of death a low output of adrenaline which was subnormal for the stress imposed by the burn. In general, these patients at first were capable of producing large quantities of adrenaline, as is seen by their initial high output. However, the adrenal medulla was apparently unable to synthesize adrenaline rapidly enough and certainly not at a rate commensurate with demand; consequently, the adrenal gland was largely depleted of its adrenaline." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC441918/pdf/jcinvest00458-0167.pdf>]

81. In a study conducted by Jack Barchas of the Semel Institute for Neuroscience & Human Behavior, University of California Los Angeles, a decreased turnover of adrenaline (epinephrine) was found in rats exposed to chronic stress. "Following acute cold swim stress, hypothalamic epinephrine (adrenaline) concentrations were markedly lowered and remained decreased for 24 h, while norepinephrine concentrations were decreased, but returned to baseline within 14 h. With oscillation stress repeated daily for 21 days, hypothalamic (brain) norepinephrine, hypothalamic epinephrine, and hippocampal norepinephrine turnover were decreased and absolute concentrations were increased. These results suggest that hypothalamic epinephrine concentration and turnover are particularly responsive to acute and chronic stress. The decreased epinephrine and norepinephrine turnover under chronic stress may be responsible in part for the behavioral and endocrine changes observed in chronically stressed rats." [<http://www.ncbi.nlm.nih.gov/pubmed/6178468>]

➤ Evidence of the Link Between Depleted Adrenaline (Epinephrine) Levels and Reduced Cell Respiration within the Cell Mitochondria, Specifically Relating to the Krebs' Citric Acid Cycle and Oxidative Phosphorylation

82. In a study conducted by the Department of Biochemistry, Faculty of Science, M.S. University of Baroda, India, researchers depleted adrenaline (epinephrine) reserves in the adrenal glands of animals using reserpine and found a decrease in liver, brain and heart mitochondrial cellular respiration. "Regulation of mitochondrial functions in vivo by catecholamines [epinephrine and norepinephrine] was examined indirectly by depleting the catecholamines stores by reserpine treatments of the experimental animals. The epinephrine (adrenaline) and norepinephrine contents in the adrenals decreased by 68 and 77% after reserpine treatment. Reserpine treatment resulted in decreased respiratory [cell] activity in liver and brain mitochondria with the two NAD<sup>+</sup>-linked substrates [occurring in the Krebs' Citric Acid Cycle]: glutamate and pyruvate + malate with succinate ATP synthesis rate decreased in liver mitochondria only. For the heart mitochondria, state 3 respiration rates [of the Citric Acid Cycle] decreased for all substrates." [<http://www.ncbi.nlm.nih.gov/pubmed/11081415>]

83. In a study conducted by the Department of Medicine and Pharmacy, University of Poitiers, researchers found adrenaline (epinephrine) increased cellular respiration significantly within the mitochondria of liver cells. "We studied the effects and mode of action of epinephrine (adrenaline) on the oxidative phosphorylation of rat liver [cell] mitochondria. With either succinate or beta-hydroxybutyrate as substrate, i.v. injection of 1.5 microgram/100 g epinephrine (adrenaline) increased the respiratory rates by 30-40% in state 3 (with ADP), and by 20-30% in state 4 (after ADP phosphorylation), so that the respiratory control ratio (state 3/state 4) changed little. The respiratory stimulation by epinephrine (adrenaline) was maximal 20 minutes after its injection. Epinephrine (adrenaline) therefore has an alpha 1-type of action on mitochondrial oxidative phosphorylation." [<http://www.ncbi.nlm.nih.gov/pubmed/2888518>]

84. A study conducted by the Department of Biochemistry, University of Cambridge, UK found adrenaline has a direct affect on most operating systems within the cell, particularly cell respiration. "Hepatocyte (liver cell) metabolism was divided into nine reaction blocks: glycogen breakdown, glucose release, glycolysis, lactate production, NADH oxidation, pyruvate oxidation, proton leak, mitochondrial phosphorylation and ATP consumption, linked by five intermediates: mitochondrial membrane potential, cytoplasmic NADH/NAD and total cellular ATP, glucose 6-phosphate and pyruvate. In this study, the changes in flux and intermediate levels that occurred upon addition of either glucagon or adrenaline were measured. From comparison of the fractional changes in fluxes and intermediate levels with the known kinetics of the system, it was possible to determine the primary sites of action of the hormones. The results show that the majority of processes in the cell are responsive to the hormones [adrenaline and glucagon]. The notable exception to this is the failure of adrenaline to have a direct effect on glycolysis." [<http://www.ncbi.nlm.nih.gov/pubmed/10518800>]

85. In a study conducted by the Department of Biochemistry, Second Military Medical College, Shanghai, PR China, researchers found adrenaline (epinephrine) increased cellular respiration and ATP energy production within cell mitochondria. "Thirty minutes after Sprague-Dawley rats had been injected subcutaneously with epinephrine (adrenaline) or norepinephrine, the respiratory control ratio (RCR), the rate of O<sub>2</sub> consumption in state 3 and the rate of ATP [energy] formation in liver [cell] mitochondria succinate respiratory chain were increased. Compared with our previous results, it can be suggested that catecholamines [epinephrine and norepinephrine] may play an important role in the increase of oxidative phosphorylation coupling in the early phase of burn injury." [<http://www.ncbi.nlm.nih.gov/pubmed/8471141>]
86. In a landmark study of eight men conducted by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, researchers found adrenaline (epinephrine) doubled the Krebs' Citric Acid Cycle mitochondrial respiratory output of citrate, malate and fumarate. "The effects of epinephrine (E) and insulin infusions on the contents of tricarboxylic acid cycle (Citric Acid Cycle) intermediates, adenine [cellular respiration] nucleotides and their catabolites [used to break down molecules into ATP energy], and amino acids in skeletal muscle have been investigated. Eight men were studied on two separate occasions: 1) during 120 min of euglycemic hyperinsulinemia (insulin infusion-UH) and 2) during UH (insulin infusion) while E (epinephrine) was infused. The sum of [Citric Acid Cycle] citrate, malate, and fumarate in muscle did not change significantly during UH (insulin infusion) but doubled during UHE (insulin + epinephrine infusion). It is concluded that E (epinephrine) infusion increases the contents of TCAI (Citric Acid Cycle intermediates) in human skeletal muscle, and it is likely that at least part of the increase is attributable to increased flux through the ALT (alanine aminotransferase) reaction." [<http://www.ncbi.nlm.nih.gov/pubmed/2003596>]
- Evidence of the Link Between Reduced Respiration within the Cell Mitochondria and Increased Cell Glucose Fermentation [via the Process known as Glycolysis]
87. In a study by the Department of Molecular Pathology, The University of Texas MD Anderson Cancer Center, researchers found the deliberate damaging of mitochondrial cell respiration caused a shift from oxidative phosphorylation to glucose fermentation via the process known as glycolysis. "Elevated aerobic glycolysis in cancer cells (the Warburg effect) may be attributed to respiration injury or mitochondrial dysfunction, but the underlying mechanisms and therapeutic significance remain elusive. Here we report that induction of mitochondrial respiratory defect by tetracycline-controlled expression of a dominant negative form of DNA polymerase  $\gamma$  causes a metabolic shift from oxidative phosphorylation to glycolysis and increases ROS [the damaging of cells via oxidative stress] generation." [<http://www.ncbi.nlm.nih.gov/pubmed/22589701>]
88. In a study conducted by the State Key Laboratory of Oncology in Southern China, Sun Yat-Sen University Cancer Center, researchers also found the deliberate damaging of mitochondrial cell respiration increased glucose fermentation. "Increased aerobic glycolysis (glucose fermentation) and oxidative stress are important features of cancer cell metabolism, but the underlying biochemical and molecular mechanisms remain elusive. Using a tetracycline inducible model, we show that activation of [the oncogene] K-ras(G12V) causes mitochondrial [cell] dysfunction, leading to decreased [cell] respiration, elevated glycolysis, and increased generation of reactive oxygen species (ROS). Furthermore, pre-induction of [oncogene] K-ras(G12V) expression in vitro to allow metabolic adaptation to high glycolytic metabolism enhances the ability of the transformed cells to form tumor in vivo." [<http://www.ncbi.nlm.nih.gov/pubmed/21876558>]
89. In a study conducted by Seahorse Bioscience, Massachusetts, researchers found cancer cells have reduced mitochondrial cell respiration and a dependency on glucose fermentation. "Increased conversion of glucose to lactic acid [via glycolysis fermentation] associated with decreased mitochondrial respiration is a unique feature of tumors first described by Otto Warburg in the 1920s. Using a novel approach to measure cellular metabolic rates in vitro, the bioenergetic basis of this increased glycolysis and reduced [cell] mitochondrial respiration was investigated in two human cancer cell lines, H460 and A549. The bioenergetic phenotype was analyzed by measuring cellular respiration, glycolysis rate, and ATP [energy] turnover of the cells in response to various pharmacological modulators. H460 and A549 [cancer] cells displayed a dependency on glycolysis and an ability to significantly upregulate this pathway when their respiration was inhibited. The converse, however, was not true. The [cancer] cell lines were attenuated (reduced) in oxidative phosphorylation (OXPHOS) capacity and were unable to sufficiently upregulate mitochondrial OXPHOS when glycolysis was disabled. This observed mitochondrial impairment was intimately linked to the increased dependency on glycolysis. In summary, our results demonstrate a bioenergetic phenotype of these two cancer cell lines characterized by increased rate of glycolysis (glucose fermentation) and a linked attenuation (reduction) in their OXPHOS (oxidative phosphorylation) capacity." [<http://www.ncbi.nlm.nih.gov/pubmed/16971499>]

90. In a key study conducted by the Genome Integrity Unit, Danish Cancer Society Research Center, researchers found cancer cells are addicted to glycolysis (glucose fermentation) and to the oncogene that sustains glycolysis, for ATP energy production due to impaired mitochondrial cell respiration. "Oncogene addiction describes how cancer cells exhibit dependence on single oncogenes to escape apoptosis (cell death) and senescence (aging). Here we provide evidence for a metabolic rationale behind the addiction to [oncogene] (V600E)BRAF in two malignant melanoma cell lines. Both cell lines display a striking addiction to glycolysis (glucose fermentation) due to underlying dysfunction of oxidative phosphorylation (OXPHOS). Notably, even minor reductions in glycolytic activity lead to increased OXPHOS activity (reversed Warburg effect), however the mitochondria are unable to sustain ATP [energy] production. We show that [oncogene] (V600E)BRAF upholds the activity of glycolysis (glucose fermentation) and therefore the addiction to glycolysis de facto becomes an addiction to [oncogene] (V600E)BRAF." [<http://www.ncbi.nlm.nih.gov/pubmed/23603840>]
91. In a study conducted by the Jefferson Stem Cell Biology and Regenerative Medicine Center, Department of Stem Cell Biology and Regenerative Medicine, Thomas Jefferson University, Philadelphia, researchers found cells deficient in TFAM [a protein essential for mitochondrial respiratory cell functioning] shifted to glycolysis (glucose fermentation), increased lactic acid production and promoted tumor growth. "In this model, cancer cells induce oxidative stress in adjacent stromal fibroblasts; [cells located in connecting tissue]. This, in turn, causes several changes in the phenotype (characteristics) of the fibroblast [cells] including mitochondrial dysfunction, hydrogen peroxide production, and aerobic glycolysis, resulting in high levels of L-lactate (lactic acid) production. L-lactate is then transferred from these glycolytic fibroblasts (glucose fermenting normal tissue cells) to adjacent epithelial cancer cells and used as "fuel" for oxidative mitochondrial metabolism. To synthetically generate glycolytic fibroblasts (glucose fermenting normal tissue cells), we genetically-induced mitochondrial [cell] dysfunction by knocking down TFAM using an sh-RNA approach. TFAM is mitochondrial transcription factor A, which is important in maintaining the mitochondrial respiratory chain. TFAM-deficient fibroblasts [cells] showed evidence of mitochondrial dysfunction and oxidative stress, with the loss of certain mitochondrial respiratory chain components, and the over-production of hydrogen peroxide and L-lactate. Thus, TFAM-deficient fibroblasts [cells] underwent metabolic reprogramming towards aerobic glycolysis. Most importantly, TFAM-deficient fibroblasts significantly promoted tumor growth, as assayed using a human breast cancer (MDA-MB-231) xenograft model." [<http://www.ncbi.nlm.nih.gov/pubmed/22129993>]
92. In a study conducted by the Washington University School of Medicine, Department of Internal Medicine, St Louis, Missouri, researchers found brain tumors are dependent on glycolysis (glucose fermentation) due to impaired mitochondrial cell respiration. "The mitochondrial lipidome [that includes lipid vitamin A, D, E, K molecules] influences ETC (the electron transport chain --- which is the site of oxidative phosphorylation) and cellular bioenergetic efficiency. Brain tumours are largely dependent on glycolysis (glucose fermentation) for energy due to defects in mitochondria and oxidative phosphorylation. In the present study, we used shotgun lipidomics to compare the lipidome in highly purified mitochondria isolated from normal brain, from brain tumour tissue, from cultured tumour cells and from non-tumorigenic astrocytes (tumor-free brain cells). The mitochondrial lipid abnormalities in solid tumours and in cultured cells were associated with reductions in multiple ETC [cell respiration] activities, especially Complex I. The in vitro growth environment produced lipid and ETC [cell respiration] abnormalities in cultured non-tumorigenic astrocytes that were similar to those associated with tumorigenicity. These results indicate that in vitro growth environments can produce abnormalities in mitochondrial lipids and ETC [cell respiration] activities, thus contributing to a dependency on glycolysis for ATP [energy] production." [<http://www.ncbi.nlm.nih.gov/pubmed/19570033>]

➤ Evidence of the Link Between Glucose Fermentation, Tumor Growth and Increased Cell Lactic Acid Production

93. In a study conducted by the Department of Hematology and Oncology, University of Regensburg, Germany, researchers found glucose fermenting tumor cells produce high levels of lactic acid which suppress immune system T cell production and activity. "A characteristic feature of tumors is high production of lactic acid due to enhanced glycolysis (glucose fermentation). Here, we show a positive correlation between lactate serum levels and tumor burden in cancer patients and examine the influence of lactic acid on immune functions in vitro. Lactic acid suppressed the proliferation and cytokine production of human cytotoxic T lymphocytes (CTLs) up to 95% and led to a 50% decrease in cytotoxic (T cell) activity. A 24-hour recovery period in lactic acid-free medium restored CTL (T cell) function." [<http://www.ncbi.nlm.nih.gov/pubmed/17255361>]
94. In a study conducted by the Department of Radiology, University of Pennsylvania, Philadelphia, researchers found when the immune-suppressant drug rapamycin was used to inhibit lactic acid production in lymphoma cancer cells, the expression of the key enzyme hexokinase II found in glycolysis (glucose fermentation) was also inhibited. "Using human B-cell lymphoma models and MRS (magnetic resonance spectroscopy imaging),

we have demonstrated that the inhibition of the mTOR signaling pathway can be detected in malignant cells in vitro and noninvasively in vivo [in animal models] by the measurement of lactate levels. An mTOR inhibitor, rapamycin, suppressed lactic acid production in lymphoma cell line cultures and also diminished steady-state lactate levels in xenotransplants (cell tissue transplants). In xenotransplants, 2 days of rapamycin treatment produced significant changes in lactic acid concentration in the tumor measured in vivo, which were followed by tumor growth arrest and tumor volume regression. The rapamycin-induced changes in lactate (lactic acid) production were strongly correlated with the inhibition of expression of hexokinase II, the key enzyme in the glycolytic (glucose fermentation) pathway." [<http://www.ncbi.nlm.nih.gov/pubmed/22711601>]

95. In a study conducted by the Institute for Physical Chemistry, University of Düsseldorf, Germany, researchers found tumor cells deprived of oxygen and then fed glucose produced five times more lactic acid than normal tumor cells. "Viability, glycolytic (glucose fermentation) capacity and energy metabolism under anaerobic conditions were studied in the hepatoma (liver tumor) cell lines HTC, FU5 and HepG2 and in rat and human hepatocytes using glucose and fructose as glycolytic precursors. During 6 hours of anaerobic incubation without additional substrate, [cell] viability decreased rapidly in FU5 and HTC cells, whereas viability of HepG2 cells was not significantly affected. In all tumor cells, 10 mmol/L glucose prevented hypoxic (deprived oxygen) cell injury almost completely. Lactate formation from glucose was about five times higher than in hepatocytes (liver cells) under these circumstances." [<http://www.ncbi.nlm.nih.gov/pubmed/1847350>]
96. In a study conducted by the Marseilles Cancer Research Centre, The National Health and Medical Research Institute, France, researchers found hypoxia (the deprivation of oxygen) increased the rate of glycolysis (glucose fermentation) in pancreatic cancer cells, causing them to switch from mitochondrial respiration to lactic acid production. "Here, using a well-defined mouse model of pancreatic cancer, we report that hypoxic areas from pancreatic ductal adenocarcinoma are mainly composed of epithelial cells harboring epithelial-mesenchymal transition (invasion) features and expressing glycolytic markers, two characteristics associated with tumor aggressiveness. We also show that hypoxia (deprivation of oxygen) increases the "glycolytic" switch of pancreatic cancer cells from oxidative phosphorylation to lactate (lactic acid) production and we demonstrate that increased lactate efflux (lactic acid release) from hypoxic cancer cells favors the growth of normoxic (normal oxygen level) cancer cells." [<http://www.ncbi.nlm.nih.gov/pubmed/23407165>]
97. In a landmark study conducted by the Department of Medicine, Case Western Reserve University, Cleveland, Ohio, researchers found in normal cells [stimulated by oxalyl chloride to ferment more glucose], the excess glucose not needed for normal cell-controlled metabolism was near-completely converted to lactic acid. "In this study we examined the metabolic fate of glucose in cells in which glucose transport is stimulated by exposure to CoCl<sub>2</sub> (oxalyl chloride), an agent that stimulates the expression of a set of hypoxia-responsive genes [genes that respond well to deprived oxygen states] including several glycolytic enzymes and the Glut-1 glucose transporter. In cells treated with CoCl<sub>2</sub>, the net increase in glucose taken up was accounted for by its near-complete conversion to lactate (lactic acid). Cells stably transfected to overexpress Glut-1 also exhibited enhanced net uptake of glucose with the near-complete conversion of the increased glucose taken up to lactate; however, the effect in these cells was observed in the absence of any change in the activity of two glycolytic enzymes examined. These findings suggest that in cells in which glucose transport is rate-limiting (controlled) for glucose metabolism, enhancement of the glucose entry step per se results in a near-complete conversion of the extra glucose to lactate." [<http://www.ncbi.nlm.nih.gov/pubmed/11888207>]

➤ Evidence of the Link Between Increased Cell Lactic Acid Production and Low pH Levels in the Cell and Body

98. In a study conducted by the Department of Clinical Physiology, Karolinska Institute, Huddinge Hospital, Sweden, researchers found pH levels in muscle tissue dropped to acidic levels as lactic acid levels increased. "Analyses were made on muscle samples taken from the lateral part of the m. quadriceps femoris of man (lactate, pyruvate, and pH) on venous blood (lactate, pyruvate) and on capillary blood (pH). Samples were taken at rest, immediately after termination of dynamic exercise and during 20 min recovery from exhaustive dynamic exercise. Muscle pH decreases from 7.08 at rest to 6.60 at exhaustion. Decrease in muscle pH was linearly related to muscle content of lactate + pyruvate." [<http://www.ncbi.nlm.nih.gov/pubmed/13343>]
99. In a study conducted by the Institute of Cell Biology (Cancer Research), West German Cancer Center Essen, University of Essen Medical School, researchers induced glycolysis (glucose fermentation, causing lactic acid production) in 292 rats after transplanting tissue from human cancer cell lines into their bodies and observed a significant drop in pH. "pH frequency distributions of tumours grown s.c. from 30 human tumour xenograft lines in (T-cell deficient) rats were analysed with the use of H<sup>+</sup> ion-sensitive semi-microelectrodes prior to and following stimulation of tumour cell glycolysis by i.v. infusion of glucose. At normoglycemia (normal



glucose levels), the average pH of the tumours investigated was [acidic at] 6.83 (range, 6.72-7.01; n = 268). Without exception, all [tumor cell tissue] xenografts responded to the temporary increase in plasma glucose concentration from 6 to 30 mM by an accumulation of acidic metabolites, as indicated by a pH reduction to an average value of 6.43 (range, 6.12-6.78; n = 292)." [<http://www.ncbi.nlm.nih.gov/pubmed/8353039>]

100. In a study conducted by the Dept of Radiation Medicine, Massachusetts General Hospital, Harvard Medical School, researchers found of two breast cancer cell lines, the one fermenting more glucose with higher lactic acid production had lower pH scores than the other, though both had low pH. "Glucose uptake, lactate release, ketone body utilization, spatial distribution of glucose, lactate, and ATP concentrations, as well as tissue pH distributions were systematically investigated in s.c. and/or "tissue-isolated" human breast cancer xenografts in T-cell-deficient rats. The average glucose uptake was [higher] 0.37  $\mu\text{mol/g/min}$  in medullary and [lower] 0.26  $\mu\text{mol/g/min}$  in squamous cell carcinomas of the breast. Most tumors (97%) released lactate [acid] in an amount linearly related to glucose consumption. The lactate production of medullary (0.33  $\mu\text{mol/g/min}$ ) and squamous cell (0.31  $\mu\text{mol/g/min}$ ) breast cancers was similar. The mean tissue pH in medullary breast cancers [with higher lactic acid] was [lower at] 6.81. Compared with these values, tissue pH distribution in squamous cell breast cancers [with lower lactic acid] was shifted to significantly higher values. The mean pH of the latter tumors was 7.04." [<http://www.ncbi.nlm.nih.gov/pubmed/3191497>]
101. In a study conducted by the Department of Physiology, Karolinska Institute, Stockholm University College of Physical Education and Sports, researchers found the addition of lactic acid to cell mitochondria decreased intracellular pH and cell respiration. "Mitochondrial respiration and transmembrane potential ( $\Delta\psi(m)$ ) were measured with pyruvate and malate as the substrates. The addition of lactic acid decreased the pH of the [cell] reaction medium from 7.5 to 6.4. When lactic acid was added to nonphosphorylating mitochondria, the subsequent maximal ADP-stimulated [mitochondrial] respiration decreased by 27% compared with that under control conditions." [<http://www.ncbi.nlm.nih.gov/pubmed/10444405>]
102. In a study conducted by the Department of Physiology, The University of Hong Kong, researchers found the intracellular pH of muscle cell fibres decreased with increasing levels of lactic acid. "We investigated the effects of graded doses of lactic acid on the intracellular pH and adenosine [energy] output from superfused bundles of about 15 skeletal muscle [cell] fibres. Intracellular pH was 7.07 +/- 0.05 under control conditions, which was around 0.35 units lower than extracellular pH, and adenosine output was 63 +/- 10  $\text{pmol/min/g}$ . Lactic acid produced dose-dependent decreases in intracellular pH and dose-dependent increases in adenosine output: 10 mM lactic acid decreased intracellular pH to 6.57 +/- 0.04 and increased adenosine [energy] output to 159 +/- 34  $\text{pmol/min/g}$ ." [<http://www.ncbi.nlm.nih.gov/pubmed/10983866>]
103. In a study conducted by the Department of Surgery and Physiology, University of Kentucky, researchers found intracellular pH decreased when lactic acid levels passed a certain threshold. "A narrow transition zone, during which ischemic (deprivation of blood oxygen supply) intracellular pH decreased precipitously with increasing brain lactate, was observed between 17 and 22  $\text{mumol/g}$  [lactic acid]; below 17  $\text{mumol/g}$ , intracellular pH remained stable at 6.8-6.9, whereas above 22  $\text{mumol/g}$  [lactic acid], intracellular pH decreased maximally to about 6.2. The marked decrease in intracellular pH that occurs when brain lactate surpasses 17  $\text{mumol/g}$  suggests that this sudden drop in intracellular pH may account for the "lactate threshold" for increased cerebral ischemic damage." [<http://www.ncbi.nlm.nih.gov/pubmed/2349598>]
104. In a study conducted by the Department of Pharmacology & Therapeutics, Nagoya City University, Japan, researchers found increasing lactic acid within muscle cells decreased intracellular pH. "Effects of lactate on changes in intracellular pH (pHi) and contractility during simulated ischemia and reperfusion were examined in single myocytes (muscle cells) of the guinea pig cardiac [heart] ventricle. The pHi (intracellular pH) was decreased by the simulated ischemia (deprivation of blood oxygen supply) from approx. 7.3 to approx. 6.9 regardless of lactate concentration, while the rate of pHi (intracellular pH) decrease was increased by lactate in a concentration-dependent manner." [<http://www.ncbi.nlm.nih.gov/pubmed/10496335>]

➤ Evidence of the Link Between Cancer, Tumor Growth and Depleted Adrenaline (Epinephrine) Reserves

105. In a landmark study conducted by the Department of Tumor Biochemistry, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan, researchers found clinical doses of adrenaline (epinephrine) inhibited cancer cell growth and restored cAMP (the signal messenger produced by ATP energy that regulates entry of adrenaline and glucagon into the cell). "In oral and maxillofacial surgery, epinephrine is routinely used for cancer resection and it is important to clarify the effects of this agent on cancer. We found here that the clinically relevant concentrations of epinephrine (10, 50 and 100  $\mu\text{g/ml}$ ) decreased the invasion ability of

oral squamous carcinoma (Sa3) cells. In the Sa3 cells treated with epinephrine (10, 50 and 100 microg/ml), migration, morphological changes and formation of actin stress fibers were inhibited and intracellular cyclic adenosine monophosphate (cAMP) increased significantly. These findings suggest that epinephrine inhibits the invasion of cancer cells by modulating intracellular cAMP and that clinicians could use epinephrine effectively for the surgical resection of the cancer." [<http://www.ncbi.nlm.nih.gov/pubmed/11804741>]

106. In a study of rats conducted by the Department of Anatomy, Hirosaki University School of Medicine, Japan, researchers found adrenaline (epinephrine) significantly prevented tumor incidence in the early stages after the lethal cancer-causing compound known as methylcholanthrene was injected. "Effects of adrenomedullary hormone(s) on the induction and growth of fibrosarcoma by methylcholanthrene (MC) were examined. At 28 days of age, male Wistar rats were divided into four groups: 1) control, 2) bilateral adrenomedullectomy (Bil. AMX) (removal of both adrenal glands), 3) right AMX + left adrenomedullary autotransplantation (AMX + AMT) (left adrenal still operational), 4) Bil. AMX (removal of both adrenal glands) + epinephrine injection (Bil. AMX + E) groups. 14 days after surgery, MC [fibrosarcoma cancer-causing] crystals were inserted underneath the dorsal skin, and in the Bil. AMX + E group, epinephrine was injected subcutaneously, twice every week. The incidence of tumor at 90 days after the MC injection was 8 per 35 cases (22.9%) in the control group [where the adrenals were left in-tact & still producing adrenaline], 12 per 36 cases (33.3%) in the AMX + AMT group [where the left adrenal gland was functional, still producing adrenaline], 8 per 28 cases (28.6%) in the Bil. AMX + E group [where adrenaline was injected twice weekly], and each value was lower compared with that of the Bil. AMX group, 24 per 34 cases (70.6 %), [where no source of adrenaline was available]. Since norepinephrine remaining in the blood of AMX rats was ineffective, at least it is likely that this inhibitory effect of epinephrine is mediated via the beta2-receptor. The results suggest that adrenomedullary hormone, probably epinephrine, has inhibitory effects on the induction and growth of fibrosarcoma by MC, particularly in the early stage." [[http://www.nel.edu/pdf/\\_26\\_2/NEL260205\\_PMid15855881\\_Yanagisawa\\_.pdf](http://www.nel.edu/pdf/_26_2/NEL260205_PMid15855881_Yanagisawa_.pdf)]
107. In a study conducted by the Ministry of Health, Russia, researchers found adrenaline (epinephrine) was able to prevent tumor cell division for up to 4 hours in mice against the highly malignant and rapid growing tumor known as Ehrlich's ascites carcinoma (EAC), comparable with the potent EAC repelling compound "chalone" that also inhibits tumor cell growth. "The biphasic circadian rhythm of mitotic (cell division) activity has been demonstrated in a 5-day Ehrlich's ascites carcinoma (EAC) in mice. Adrenaline injected intraperitoneally in a dose of 1.5 micrograms/g bw produced an inhibitory effect on cell division that lasted over 4 hours and reached maximum at injection to mice during light time of the day. EAC (chalone) extract in a dose of 1 ml also inhibited the mitosis during 4 hours. Combined administration of adrenaline and the extract resulted in the phenomenon of prolonged inhibition of cell division that persisted for maximum 6-8 hours, if the preparations were injected in the middle of the day light time. Of definite importance was the rhythm of changes in the sensitivity of proliferating tumor cells." [<http://www.ncbi.nlm.nih.gov/pubmed/6216926>]
108. In a study conducted by Groupe Biologie et Thérapie des Cancers, Faculty of Medicine, France, researchers found adrenaline (epinephrine) combined with chemotherapy drug cisplatin was able to effect a complete cure of cancer, where cisplatin alone was not. "Despite the theoretical advantages of a high local concentration of anti-cancer drugs, local chemotherapy often fails to produce complete and lasting responses in experimental and human solid tumors. Platinum concentration evaluated by micro-PIXE in s.c. DHD/K12/ PROb colon tumors or by atomic absorption spectrometry in DHD/K12/PROb peritoneal tumors was 4- to 12-fold higher when epinephrine (adrenaline) was added to local cisplatin. Peri-tumoral or intra-tumoral injection of cisplatin (2 mg/kg) alone does not cure s.c. DHD/K12/PROb colon tumors or GV1A1 glioma tumors in BD IX rats. By contrast, a complete and lasting cure of s.c. tumors was achieved regularly and without skin necrosis when epinephrine (adrenaline) was added to intra-tumoral or peri-tumoral cisplatin. Rats with peritoneal-tumor nodules 1 to 2 mm in diameter, and insensitive to i.p. cisplatin alone, were cured when the anti-cancer drug was combined with epinephrine (adrenaline). These experimental results could justify clinical trials using a combination of cisplatin and epinephrine (adrenaline) in the treatment of locally growing solid tumors." [<http://www.ncbi.nlm.nih.gov/pubmed/10328233>]
109. In a study conducted by the Department of Radiation Oncology, School of Medicine, Tokai University, Japan, researchers found adrenaline (epinephrine) significantly inhibited cancer growth when used with irradiation and hyperthermia treatment. "The retarding effects of hyperthermia on tumor growth and skin reactions were lost 2 days after irradiation. However, when PEP or epinephrine was injected before hyperthermia, tumor growth was distinctly delayed. The effect of epinephrine was greater than PEP and still showed enhancement 8 days after irradiation. Lung metastasis was significantly inhibited by the addition of epinephrine either 0 or 2 days after irradiation." [<http://www.ncbi.nlm.nih.gov/pubmed/9300977>]

# The 3<sup>rd</sup> Phase of Cancer



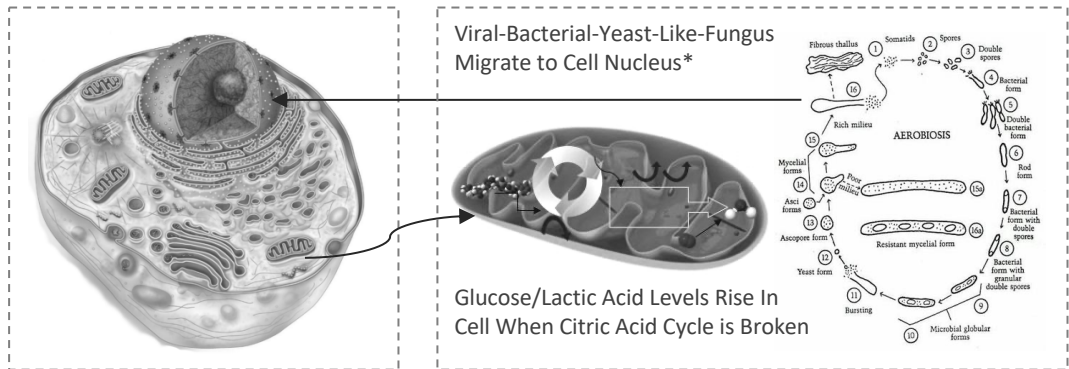
## Phase

# 3

Somatids Pleomorphise into Yeast-Like-Fungus to Ferment Excess Glucose and Lactic Acid in Cells, Causing Cell Nucleus DNA Mutation & Cancer

During phase 3, somatids (tiny microorganisms necessary for life) that live in our body pleomorphise [or change] into yeast-like-fungus to ferment excess glucose and lactic acid in cells. In a healthy person, somatids are limited to 3 stages in their life cycle – somatid, spore, double spore. However, in a highly acidic low pH lactic acid environment, somatids pleomorphise into a further 13 stages. These stages include viral-bacterial-yeast-like-fungus forms which ferment excess glucose and lactic acid in the cell. These fungal pathogenic forms then migrate to the cell nucleus to reproduce, releasing acidic waste products called “mycotoxins”, inhibiting cell DNA repair and inhibiting the all-important tumor suppressor genes. Without the tumor suppressor genes [namely p53] to regulate cell death (apoptosis) when the cell has mutated beyond repair, the cell lives on and ‘cell-growth regulating’ proto-oncogenes turn into oncogenes, causing normal cells to mutate into cancer cells.

\*Viral-Bacterial-Yeast-Like-Fungus release acidic waste products called *Mycotoxins* into the cell nucleus, inhibiting cell DNA repair and inhibiting tumor suppressor genes causing cell mutation and cancer

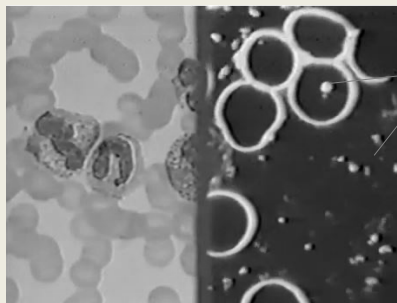


## The Theory

Over the past few centuries leading microbiologists from all over the world have discovered a tiny microorganism necessary for life that underpins all life, including all stem cell and viral-bacterial growth. This tiny microorganism has been given many names including the Somatid, the Microzyma, the Bione, the Sanal/P-Microcell/Granule, the Protit and the Turquoise Blue Granule. These “somatids” are so small they appear invisible under normal microscopic lens, and require high magnification equipment to see their naturally active moving state. A common feature of these somatid life forms, observed uniformly, is their ability to pleomorphise (change) into viral-bacterial-yeast-like-fungus forms under low pH acidic conditions. Microbiologists who have identified these somatid life forms include Antoine Béchamp [Professor of Chemistry at the University of Strasbourg]; Arthur Isaac Kendall PhD [Director of Medical Research, Northwestern University Medical School Chicago]; Royal Raymond Rife PhD [inventor of the high-magnification Rife Microscope]; Edward C Rosenow, Sr [who served as Director of Experimental Biology for the Mayo Clinic between 1915 and 1944]; Bong-Han Kim [medical surgeon at Pyongyang Medical University and Kyung-Rak institute who is widely recognized to have discovered the primo-vascular system]; Kwang-Sup Soh [professor at the Biomedical Physics Laboratory, School of Physics, Seoul National University, South Korea]; Wilhelm Reich [Deputy Director of the Vienna Ambulatorium, Sigmund Freud's psychoanalytic outpatient clinic]; and Professor Günther Enderlein [zoologist], amongst many others. The most recent of these academics to discover the existence of this living organism is Professor Gaston Naessens of France who coined the term “somatid” to describe these small bodies. Professor Naessens found when cell tissue is healthy, [these somatids that live in the tissue and blood as well as the intracellular cytosol of the cell] are limited to 3 stages – somatid, spore, and double spore; however when the cell environment is acidic and the immune system impaired, these tiny microorganisms pleomorphise into a further 13 viral-bacterial-yeast-like-fungus stages to ferment excess glucose and lactic acid, causing cancer. These fungal pathogenic forms migrate to the cell nucleus to reproduce, releasing acidic waste products called “mycotoxins”, inhibiting cell DNA repair and inhibiting the all-important tumor suppressor genes. Without tumor suppressor genes [namely p53] to regulate cell death (apoptosis) when the cell has mutated beyond repair, the cell lives on and ‘cell-

growth-regulating' proto-oncogenes turn into oncogenes, causing normal cells to mutate into cancer cells. While Professor Naessens observed these viral-bacterial-yeast-like-fungus forms were the cause of cancer within the body, he is not however the first to have observed the connection between cancer and these microbes. In 1890 William Russell [pathologist in the School of Medicine at the Royal Infirmary in Edinburgh] found parasitic yeast-like fungus organisms within all forms of cancer he examined, which ranged from barely visible to "half again as large as a red blood corpuscle". In 1901, Harvey Gaylord of New York State Pathological Laboratory of the University of Buffalo confirmed Russell's research, finding small to large parasitic forms in every cancer he examined and published a report in the American Journal of the Medical Sciences titled "The Protozoon of Cancer". In the 1920s, James Young [an obstetrician from Scotland] was able to grow pleomorphic viral-bacterial stages from various cancers which he found had a specific life cycle and spore stages. In 1925, John Nuzum [pathologist and physician at the University of Illinois, College of Medicine] isolated pleomorphic virus-like bacteria from 38 of 41 early stage breast cancers and was able to induce breast cancer in 2 of 5 dogs injected with these microbes. In 1932, Royal Raymond Rife [granted an honorary Doctor of Parasitology by the University of Heidelberg Germany for his work in making all the photo-micrographs for the "Atlas of Parasites"] cultured a viral-bacterial microorganism from a human breast cancer which he injected into 412 healthy rats which all developed breast cancer without fail. He subsequently found this microbe morphed into various viral-bacterial-yeast-like-fungus forms. In the 1940-1950s, Virginia Livingston [first female resident physician at a New York hospital, assigned to study bacterial infection], microbiologist Eleanor Alexander Jackson PhD [awarded the A. Cressy Morrison Prize by the New York Academy of Sciences for discovering certain forms of tubercle bacteria] and Irene Diller of the National Cancer Institute Fox Chase Cancer Center, Philadelphia collaborated together after each independently observing the microbe in cancer. After culturing the viral-bacterial microbe from human breast cancer tissue and re-injecting it into mice, they found the incidence of cancer doubled. Since then mainstream medicine has discovered the human papillomavirus (HPV) to be the cause of cervical cancer and head, neck and throat cancer; helicobacter pylori c. bacteria to be the cause of stomach cancer; hepatitis B and C virus to be the cause of liver cancer; and schistosoma hematobium (bilharziasis) bacteria to cause bladder cancer.

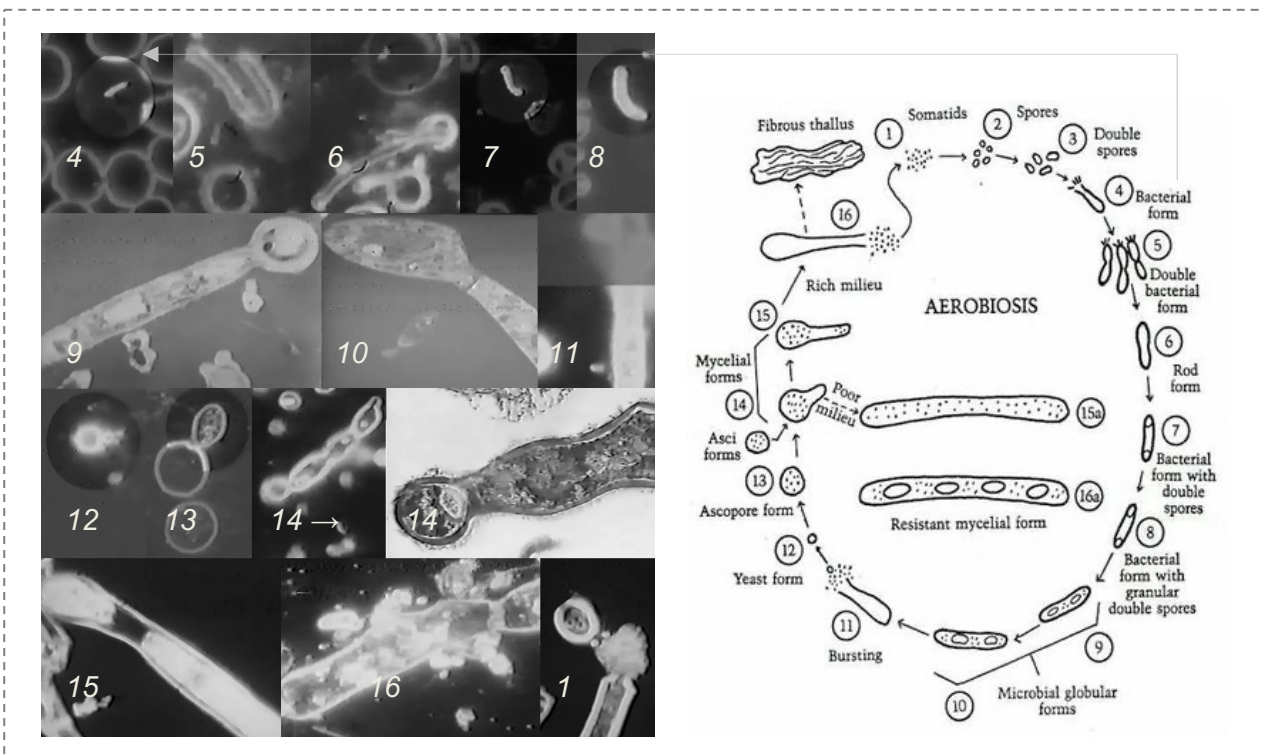
Professor Gaston Naessens: "A somatid is a basic living particle. It is indispensable to life. Without it, cellular division can't take place. It is polymorphic [meaning it can grow from one form to another, from a virus to a bacterium to a fungus]. We were able to grow it in a culture and that's where we observed its polymorphism in two cycles. First there is a micro-cycle during which the reproductive hormone that permits cellular division is developed. This [healthy 3 stage] cycle is stopped by inhibitors in the blood and during certain illnesses, including degenerative diseases. This micro-cycle, in 3 stages keeps going and becomes a 16 stage cycle [during illness]. In 1949 when I was working in haematology I had the feeling I wasn't seeing everything there was to see in blood. I saw something moving, but I didn't know what it was. I concentrated on the problem of light wave-lengths. That's how I perfected a system that gave me very worthwhile results and which enabled me to develop a microscope that allows us to see this famous particle. Little by little I was able to observe it and I extracted it from the blood. I was able to isolate it and grow it in a culture and that's how I established its polymorphism.



*The Somatid (3 stage micro-cycle) inside a blood cell and within the blood swim around at fast speed*

For more than a century the traditional method of examining blood has consisted of smearing it onto a slide, fixing it and staining it, to determine the tinctorial affinities (properties) of the elements it contains. On the left [above] we can see blood prepared according to this method. We can identify the red corpuscles, white corpuscles and platelets. This is dead blood. On the right we are seeing blood through a somatoscope. This is living blood examined within 10 minutes after it was drawn. We can see red corpuscles, white corpuscles, platelets and somatids, which we couldn't see on the fixed slide. In the course of this [somatid]

micro-cycle, a growth hormone is formed that is indispensable to cellular division. This phenomenon has been observed repeatedly in in-vitro cultures. If under the effects of stress or for that matter any biological stressor the blood's [immune] inhibitors are diminished to any considerable degree, the somatids' micro-cycle evolves into a cycle that is both different and polymorphic. We then see the appearance of the various stages of a macro-cycle – 13 additional stages in all. First we notice a bacterial form that is the normal evolution of the micro-cycle [in stage 4] where the inhibitors have been diminished. This endogenous bacterial form has been observed by many researchers. The double bacteria which evolves [in stage 5] from the preceding bacterial form is often observed in blood smears. Its particularity is the ability to divide itself by scissiparity to form rods. The rod form [stage 6] looks like a bacterial form except that it is longer and its cytoplasm seems empty. It should be noted this [next] bacterial form [in stage 7] possesses two terminal spores. The granulated double-spore bacterial form [seen in stage 8] has a cytoplasm filled with granulations that begin to move. The maturation of the granulated double-spore bacterial form [in stage 9] results in a mycobacteria well-known to microbiologists. The cytoplasm is also self-developing. The mycobacteria that we have just seen [in stage 10] has developed further and formed bubble-like enclaves to which it owes its name: bubble-mycobacteria. Here we see the bursting of the bubble-mycobacteria [in stage 11] and the release of its elements of its cytoplasm into the medium. The yeast-like formations that result [in stage 12] from the bursting of the bubble-mycobacteria, have a diameter of 4-5 microns. The yeast-like formations proliferate and become ascospore forms [in stage 13], pre-cursors of mycelial elements. From an asci form we can observe the formation of a phallus [in stage 14] in which the cytoplasm gradually takes shape to constitute the young mycelial form. It is through a conjuncture and with peristaltic movements that the young mycelia form develops a phallic cytoplasm and eventually becomes an adult mycelia form [in stage 15]. When this mycelial form element reaches full maturity [in stage 16] its cytoplasm is extremely active and when it bursts it releases an enormous quantity of new [somatid] particles into the medium, each [new] particle capable of duplicating the entire cycle."



Antoine Béchamp, who replaced Louis Pasteur as Professor of Chemistry at the University of Strasbourg, was among the first to discover the somatid [which he called the microzyma]. Béchamp demonstrated in his experiments that the somatid evolves into viral-bacterial-yeast-like-fungus forms out of a natural programmed response to a disturbed

cellular environment, to ferment either excess glucose or excess carbonic acid or lactic acid. And this is important for the cancer patient, as during prolonged chronic stress the Krebs' Citric Acid Cycle is broken and glucose and lactic acid levels rise sharply within the cell causing the somatid to pleomorphise into cancer-causing viral-bacterial-yeast-like-fungus. In a landmark year-long experiment, Béchamp demonstrated that the somatid remains only in the viral-bacterial-yeast-like-fungus state up until all lactic acid and most glucose is fermented and thus removed from the organism. At that point the viral-bacterial-yeast-like-fungus forms disappear, devolving back into the somatid.

Antoine Béchamp: "The cellularists, regarding the cellule (cell) as the simplest anatomical element, believed that it proceeded necessarily from a former cell, holding it to be the vital unit, and regarded an organism as the sum of these units. But we now know that that was a deduction from incomplete and superficial observations, for the cellule, a transitory anatomical element, has the microzyma (somatid) for its anatomical element. It is this which alone possesses all the characteristics of an anatomical element, and which must be regarded as the unit of life. It is what I have already stated in the following terms: "The microzyma (somatid) is at the beginning and at the end of every living organization. It is the fundamental anatomical element whereby the cellules, the tissues, the organs – the whole organism – can be defined as living."

The living being, filled with microzymas (somatids), carries in itself the elements essential for life, disease, death and destruction. This is because the cause of our diseased condition is always within ourselves. The microzymas (somatid) are organized ferments, and they can under favourable [highly acidic and immune deficient] conditions produce bacteria. Under other circumstances they become builder of cellules. All organisms are created by them. In short, the cellule, the bacterium itself, can *re*-become a microzyma (somatid), and thus the microzymas (somatid) are seen to be the beginning and end of all organization.

The state of perfect health results from the constancy and regularity of the coordinated functioning of the organs within which the microzymas (somatid) are healthy. And it will thus be understood that the microzymas (somatid), whether of certain cellules (cells), the vitellus (embryo), or the blood, also realize after their manner the conditions of this constancy and regularity. When these conditions are no longer realized, they may undergo vibronian (curved rod-like bacterial) evolution [as seen in stage 6]. We must remember that any microzyma (somatid), before it accomplishes the evolution which produces a bacterium, passes through the evolutionary phases of microzyma (somatid) slightly changed in form, of microzyma (somatid) successively associated in twos, in threes, in several grains, etc; [this being the 3 stage somatid micro-cycle – somatid, spore, double spore].

This determined, let us take some fresh [beer] yeast and steep it in from three to four times its weight of creosated distilled water to destroy the influence of germs of the air. In this situation, at about 30°C and without any trace of air, it will for a long time disengage pure carbonic acid [and alcohol and acetic acid], preserving its form all the time. Evidently it has only been able to produce all these things at the expense of its own substance, of its contents, since its tegument (outer covering) at first remains whole. And if the process of alteration is allowed to continue, this tegument itself will disappear, and its microzymas (somatids) will become free and vibrios (curved rod-like bacterium) will appear.

The phenomenon of the spontaneous destruction of the cellules (cells) of beer yeast has enabled me to confirm the generality of the fact which I had long before observed in studying the microzymian (somatid) origin of the vibroniens (curved rod-like bacterium). While the [cell] globule of yeast is being destroyed and its microzymas (somatids) set free and begin to undergo vibronian (curved rod-like bacterium) evolution, several phases of this evolution are to be observed, which [Professor] Estor and I have described from the commencement of our researches upon the liver, etc, namely, at first the microzymas (somatid) are scarcely altered in their size and form; then microzymas (somatids) of from 3 to

10 and 20 grains, all of the same size; then vibrios (curved rod-like bacteria) properly so called; then bacteria often very large, motile (moving) or not; also the amylobacters (corkscrew bacteria), either free or fastened end to end. All of these productions may be seen at the same time in the field of the microscope. Now if without changing any of the conditions of the experiment the observation of it is continued, it will be seen that all the [viral-bacterial-yeast-like-fungus] forms other than the single microzymas (somatid) disappear successively; for the amylobacters disappear; then new forms of smaller dimensions appear and disappear in turn, so that in the end there remain only swarms of motile (moving) forms scarcely differing from the original microzymas (somatids) which had evolved. Speaking then in the language of anatomy, we may say that the microzymas (somatids) become vibrioniens (rod-like bacteria) by evolution; the vibrios, the bacteria, the vibrioniens (viral-bacterial-yeast-like-fungus) in general, return to the microzymas (somatid) form by an inverse phenomenon of evolution.

I recall the facts that [Professor] Ester and I, in our note, described an experiment from which we concluded that in the presence of pure calcic carbonate [which subsequently produces carbonic acid in the presence of glucose-starch], and for so long as the microzymas of the fibrin (somatid of the somatid-spore) continued to evolve, they behaved as alcoholic ferment, and as ascetic, lactic and butyric ferments. The proportions of the materials employed [for this experiment] were as follows: fecula (glucose-starch) of potatoes, 5 parts, transformed into [glucose] starch in 85 per cent of water, pure calcic carbonate, 1 part; and fibrin (somatid-spores), fresh, moist, newly prepared 0.13 parts. The temperature of the oven was 35° to 40°C. The two experiments [which are two phases of the same year long experiment] were started on the 22<sup>nd</sup> of May. The next day, disengagement of gas commenced: a mixture of carbonic acid and of hydrogen. One of the experiments [the first] was stopped on the 10<sup>th</sup> of September for the purpose of making the analysis. There was still a large amount of fecula (glucose) not transformed. The products of the fermentation were: absolute alcohol (21cc), propionic acid (12g), butyric acid (150g), crystallised acetate of soda (650g) [and most importantly] crystallised lactate [acid] of chalk (709g). The second operation [of the year long experiment] was continued until the lactate [acid] formed had been [completely] transformed [by the bacterial-yeast-like-fungus]; [and] analysis of the products was made on the 10<sup>th</sup> of May of the following year. There was still some fecula (glucose) not transformed [and no presence remaining of lactate acid]. Thus, as in the classical lactic fermentations, the ferment which produced the lactic acid is also that which destroys this acid. I shall, by and by, insist further on the fact that the bacteria (yeast-like-fungus) of the microzymas (somatid) which evolve in the first [part of the experiment to ferment the glucose & lactic acid] have gradually but completely disappeared in the second [part of the experiment] so that at the end there only remained a few forms closely allied to the microzymas (somatid)."

[Excerpts from the book 'The Blood and its Third Element' by A. Béchamp]



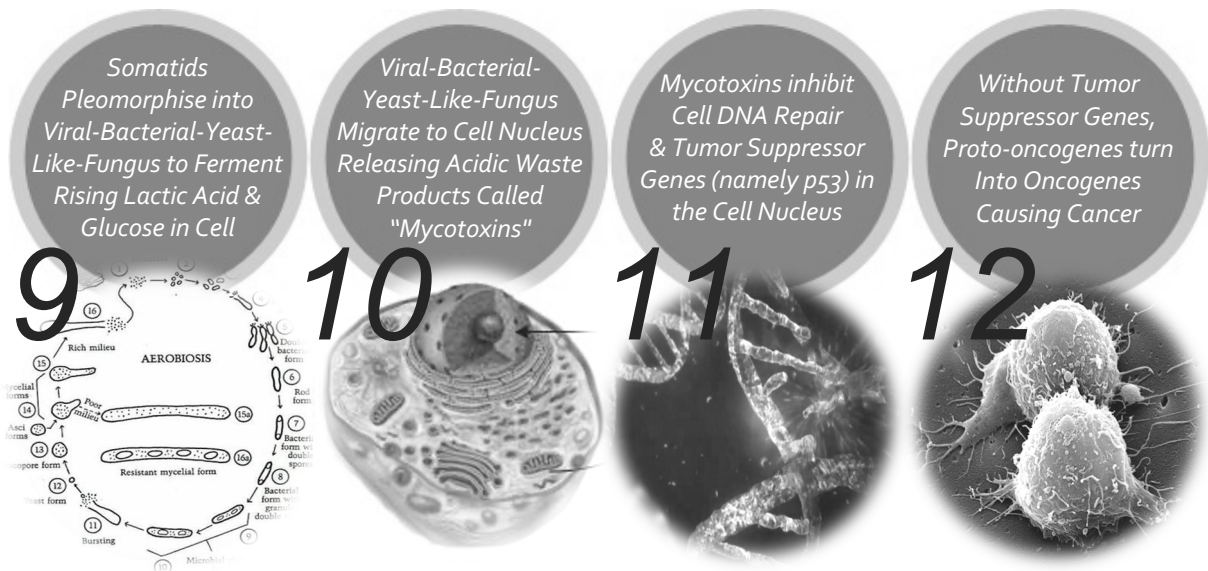
[Antoine Béchamp]

In 1983, the Holy Spirit of God revealed in the following transcript what we know as cancer is in fact seven different types of fungus. God was asked whether the following information from Spirit is valid: {"For the greatest bane of all, the cancer, here to you I give the answer --- ketone. For the prevention of cancer, use the mind, but to reassure yourself in the mortal mind take three teaspoons of vinegar once a day, anytime, any day. For the cure of the ravage (cancer), the destruction of pain, take three teaspoons a day (of vinegar), three times any time, any way". And he asks the question: "How soon will the cure be detected?" From one day to the next, but there will be complete and total remission of all traces of the disease within three days." And he asks: "How does this work?" And it responded: "For every action, there is a reaction. You should know this from your friend and mine, -- A. Einstein. The disease is an action of a mould-type fungus. The acidic acid reacts against this fungus by reversal of the growth tissues it has fed upon. It literally starves to death. Since it must feed constantly, the destruction of this fungus is quick."}

The Holy Spirit of God: "This Awareness indicates that this is valid in most cases, to a degree. This Awareness indicates that most of what is called cancer is in fact a fungus. This Awareness indicates it appears there are approximately seven different types of fungus which are diagnosed as cancer. This Awareness indicates that the use of vinegar as that which, (this particularly apple cider vinegar), has been effective in the treatment and the remission of many of these types of fungus. This Awareness indicates that it will depend on the stage of the condition and the general immunity system of the individual, whether the individual has the recuperative powers to recover with the assistance of the vinegar. This Awareness indicates also high doses of Vitamin C, the use of lemon and other anti-oxidants as has been given by this Awareness in past readings. These also are of great benefit in countering these fungus types. This Awareness indicates that there are many types of cancer, and many causes, and much of this is a psychological condition, caused by free radicals within the system that have an effect upon the metabolism, creating a dissolving of the immunity system to allow these fungi, and other elements to grow in a destructive manner within the tissue. This Awareness indicates there are many ways whereby cancer can be cured. There are many ways whereby cancer can remain incurable, depending largely on the type and the progression of the cancer. This Awareness indicates that this does however appear to be reaching a time wherein even though much vested interest prevents a single publicized common cure for all types of cancer, there are still increasing numbers of entities being cured from cancer, wherein in the past, many of these would have died." [Note: Apple cider vinegar damages tooth enamel. Therefore always dilute ACV in a large glass of water.]

[<http://cosmicawareness.org/81170.pdf>]

Within the 3<sup>rd</sup> Phase of Cancer the following sequence of events can be observed in the cancer patient:



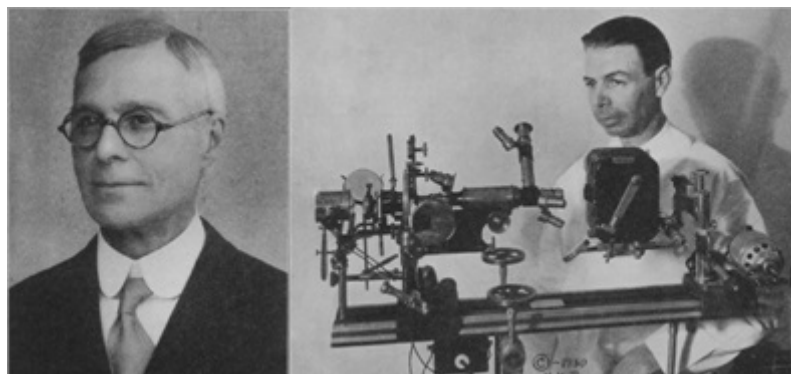


## The Evidence

The evidence for Phase 3 of Cancer can be broken down into the following components: a) the link between the somatid pleomorphising (changing) into viral-bacterial-yeast-like-fungus, b) the link between viral-bacterial-yeast-like-fungus fermenting glucose and lactic acid, c) the link between increased lactic acid fermentation in the cell and cancer, d) the link between viral-bacterial-yeast-like-fungus producing mycotoxins, e) the link between mycotoxins and cell-nucleus DNA damage, f) the link between cell-nucleus DNA damage/mutation/and inhibition of tumor suppressor genes [specifically p53, SWI/SNF] and cancer, g) the link between inhibition of tumor suppressor genes [specifically p53 and SWI/SNF] switching proto-oncogenes to oncogenes and cancer.

➤ Evidence of the Link Between the Somatid Pleomorphising (changing) into Viral-Bacterial-Yeast-Like-fungus

110. In 1931 in a groundbreaking report, Arthur Isaac Kendell PhD [Director of Medical Research, Northwestern University Medical School Chicago] and Royal Raymond Rife PhD [inventor of the high-magnification Rife Microscope] published study findings on the undeniable link between the somatid [what they called granules or small oval turquoise-blue bodies] and the growth of bacteria pleomorphising within the body, as follows: "The organism selected for these experiments was the well known [bacterial] strain of *B. typhosus*. Examined in this polarized light [of the Rife Microscope], this thrice filtered culture of *B. typhosus* cultivated in K [protein] Medium showed small, oval granules, many of them quite actively motile (in motion). These motile granules when in true focus appeared as bright turquoise-blue bodies. The qualitative results were always the same, namely, the occurrence of small, oval, actively motile, turquoise-blue bodies in the [bacterial] cultures and the absence of these small, oval, actively motile, turquoise-blue bodies in the uninoculated [bacterial-free] control K Media. From the two facts thus far arrived at, namely, that the small, oval, turquoise-blue bodies were actively motile (in motion) and also that they were cultivable from K Medium to K Medium, it is surmised that these small, oval, motile, turquoise-blue [somatid] bodies are indeed the filterable [smaller] forms of the [bacterium] *B. typhosus*. There is another even more direct procedure for establishing the identity of these small, oval, motile, turquoise-blue bodies. It has been shown in previous communications that agar cultures, or better, broth cultures of *B. typhosus* inoculated into K Medium, become filterable within eighteen hours growth at 37 degrees centigrade. Darkfield [microscopic] examination of [a further *B. typhosus*] culture revealed unchanged, actively motile bacilli (bacteria), bacilli with granules within their substance, and free swimming, actively motile granules. This culture examined in the Rife microscope showed very clearly the three types of organisms just described, namely: First, unchanged bacilli (bacteria): These were relatively long, actively motile (moving), and almost devoid of color. Second, long, actively motile bacilli (bacteria), each with a rather prominent granule at one end. The granule in such an organism was turquoise blue, reminiscent in size, shape, and color of the small, oval, actively motile, turquoise-blue [somatid] granules found in the protein medium (K Medium). These bacilli having the turquoise-blue granules were colored only at the granule end, the remainder of the rod being nearly colorless, in this respect corresponding to the unchanged [non-filterable] bacilli just mentioned. Third, free swimming, small, oval, actively motile, turquoise-blue granules, precisely similar, apparently, in size, shape, and color to those seen in the granulated bacilli just described. From the fact that these small, oval, turquoise blue bodies could be seen both in the parent rod and free swimming in the medium, it is assumed that these small, oval, actively motile, turquoise blue [somatid] bodies are indeed the filterable [smaller] form of [bacterium] *B. typhosus*." [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1658030/pdf/calwestmed00454-0001.pdf]



[Arthur Isaac Kendall (left) and Royal Raymond Rife]

111. In 1932, Edward C Rosenow, Sr [who served as Director of Experimental Biology for the Mayo Clinic between 1915 and 1944] was invited by Kendall and Rife [above] to conduct his own experiment and concluded

unequivocally the existence of the somatid and its role in bacterial pleomorphism, as follows: "Recently, I reported to the staff of the Mayo Clinic the more important observations made during three days, July 5, 6 and 7, 1932, spent in Dr. Kendall's laboratory at Northwestern University Medical School, Chicago. I went there at the invitation of Drs. Kendall and Rife, to share with them their observations in a restudy of the filter-passing forms of Eberthella typhi [the bacterium Bacillus typhosus] as seen with an improved model of the Rife microscope. They asked me also to bring with me my cultures of the [bacterial] streptococcus from poliomyelitis (polio disease). I would like to repeat here that portion of my report which had to do specifically with the Rife microscope. Owing to the novel and important character of the work, each of us verified at every step the results obtained. Microscopic examinations of suitable specimens was made as a routine by Dr. Rife with his high-power microscope, by Dr. Kendall with the oil immersion dark field [microscope], and by myself with the ordinary Zeiss microscope equipped with a 2 mm apochromatic oil immersion lens and x 10 ocular giving a magnification of about 900 diameters. Most observations with the Rife microscope were made at 8,000 diameters. In order to check the magnification, gram and safranin stained films of cultures of [the bacterium] Eberthella typhi, of the [bacterium] streptococcus from poliomyelitis, and stained films of blood, and of the sediment of the spinal fluid from a case of acute poliomyelitis (polio viral-disease), were examined. In my original report (given at Staff Meeting Mayo Clinic, 7: 408-413 July 13, 1932), I summarized as follows: There can be no question of the existence of the filterable turquoise blue [somatid] bodies of [the bacterium] Eberthella typhi described by [Dr.] Kendall. They are not visible by the ordinary methods of illumination and magnification, not because they are too small, but rather, it appears, because of their peculiar non-staining hyalin (translucent) structure. Their visualization under the Rife microscope is due to the ingenious methods employed rather than to excessively high magnification. Examination under the Rife microscope of specimens, containing objects visible with the ordinary microscope, leaves no doubt of the accurate visualization of objects or particulate matter by direct observation at the extremely high magnification (calculated to be 8,000 diameters) obtained with this instrument. The findings under the Rife microscope of cocci (spherical bacterial) and diplococci (paired spherical bacteria) in filtrates of cultures of the [bacterium] streptococcus from poliomyelitis, and in filtrates of the viruses of poliomyelitis and herpes encephalitis, not detectable by the ordinary methods of examination, and which resembled in form and size those found in the respective cultures, and the absence of minute forms, suggest that the filterable, inciting agent of these diseases is not necessarily extremely small, as is universally believed. Indeed, the filterable, inciting (causal) agent may be the non-staining, highly plastic, hyalin (translucent somatid) stage of the visible, stainable, cultivable [bacterial] organism, the streptococcus. It is, of course, possible that these unstained, invisible [somatid] forms revealed by ordinary methods of examination are not the inciting agents or "viruses" of these diseases and that they represent merely the filterable or other state of the streptococcus. A consideration of the great difficulty one has in isolating the [bacterium] streptococcus and demonstrating diplococci (the presence of paired spherical bacteria) in lesions in these diseases and the ease with which the bodies are found in the filtrate, indicate clearly that the "invisible" [somatid] forms of the streptococcus, if such they be, are present in large numbers in the host, as in positive cultures of the streptococcus. Their form, size and color are too characteristic and true to type to permit considering them as artifacts or as being expressive of etiologically unrelated contaminating streptococci. Non-infectivity of the filter-passing forms, except in the cases of virus diseases, their presence in large numbers in filtrates, both of cultures and of infected tissues, and the great difficulty in obtaining the visible forms in cultures of filtrates indicate that "invisible", filter-passing [somatid] forms represent a certain stage in the development of [viral-bacterial-yeast-like-fungus] microorganisms. EDWARD C. ROSENOW." [<http://www.sciencemag.org/content/76/1965/192.long>]



[Edward C Rosenow, Sr, 1875-1966]

➤ Evidence of the Link Between Viral-Bacterial-Yeast-Like-Fungus Fermenting Glucose and Lactic Acid

112. In a study conducted by the Department of Bacteriology, Environmental Medicine and Infectious Diseases, Kyushu University, Japan, researchers found the bacteria responsible for pneumonia converts lactic acid as part of the fermentation of glucose. "In the present study, we present data indicating that in [the bacterium] *S. Pneumonia*, lactate oxidase converts lactate (lactic acid), [usually regarded as a dead-end product of glucose metabolism in this organism] back to pyruvate, which is then subject to oxidation by pyruvate oxidase to form acetyl phosphate." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2395018/>]
113. In a study conducted by the Rowett Research Institute, Scotland, researchers found the bacteria *Eubacterium hallii* increased 100-fold by converting lactic acid to other acids in the human body. "The human intestine harbors both lactate-producing and lactate-utilizing bacteria. The effect of different initial pH values (5.2, 5.9, and 6.4) upon lactate metabolism was studied with fecal inocula from healthy volunteers. Populations of *Eubacterium hallii*, a lactate-utilizing butyrate [butyric acid]-producing bacterium, increased 100-fold at pH 5.9 and 6.4. These experiments suggest that lactate (lactic acid) is rapidly converted to acetate, butyrate, and propionate [acid] by the human intestinal microbiota [bacterium] at pH values as low as 5.9." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2075063/>]
114. In a study conducted by the Laboratory of Gastrointestinal Microbiology, College of Animal Science and Technology, Nanjing Agricultural University, China, researchers found bacteria rapidly consume and convert lactic acid to other acids within the large intestine. "A lactate-utilizing, butyrate [butyric acid]-producing bacterium, strain LB01, was isolated from adult swine feces by utilizing modified Hungate technique with rumen liquid-independent YCFA medium supplemented with lactate (lactic acid) as the single carbon source. It was an obligate anaerobic, Gram positive bacterium, and could utilize (ferment) glucose, fructose, maltose and lactate (lactic acid) with a large amount of gas products. Lactate (lactic acid) at the concentration of 65 mmol/L in YCFA medium was rapidly consumed [by the bacterium] within 9 hours and was mainly converted to propionate and butyrate [acid] after 24 hours. The metabolic characteristics that [bacterium] strain LB01 efficiently converts toxic lactate (lactic acid) and excessive acetate to butyrate [acid] can prevent lactate and acetate accumulation in the large intestine." [<http://www.ncbi.nlm.nih.gov/pubmed/17672301>]
115. In a joint study conducted by Chiba University, The University of Tokyo, the National Institute of Infectious Diseases, Japan and the University of Missouri-Kansas City, USA, researchers found the fungal-yeast *Candida glabrata* requires lactic acid assimilation to survive in hypoxic (deprived oxygen) conditions. "The intestinal resident *Candida glabrata* opportunistically infects humans. However few genetic factors for adaptation in the intestine are identified in this fungus. Here we describe the *C. glabrata* CYB2 gene encoding lactate dehydrogenase as an adaptation factor for survival in the intestine. A previous report suggested that *Cyb2p* is responsible for lactate (lactic acid) assimilation. Additionally, it was speculated that lactate assimilation was required for *Candida* virulence because *Candida* must synthesize glucose via gluconeogenesis under glucose-limited conditions such as in the host. Interestingly, [fungal-yeast] *C. glabrata* could assimilate lactate (lactic acid) under hypoxic [deprived oxygen] conditions, dependent on CYB2, but not yeast *S. cerevisiae*. Because accessible oxygen is limited in the intestine, the ability for lactate assimilation in hypoxic conditions may provide an advantage for a pathogenic yeast." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3170380/>]
116. In a study conducted by the Department of Chemical and Biological Engineering, South Dakota School of Mines and Technology Rapid City, USA, researchers found eight strain of bacteria dug up from 1.34km below the earth's surface had the ability to ferment glucose. "Eight fermentative bacterial strains were isolated from mixed enrichment cultures of a composite soil sample collected at 1.34 km depth from the former Homestake gold mine in Lead, SD, USA. Phylogenetic analysis of their 16S rRNA gene sequences revealed that these isolates were affiliated with the phylum Firmicutes belonging to genera *Bacillus* and *Clostridium* [bacterium]. Batch fermentation studies demonstrated that isolates had the ability to ferment glucose, xylose, or glycerol to industrially valuable products such as ethanol and 1,3-propanediol. Ethanol was detected as the major fermentation end product in glucose-fermenting cultures at pH 10 with yields of 0.205-0.304 g of ethanol/g of glucose." [<http://www.ncbi.nlm.nih.gov/pubmed/23919089>]
117. In a landmark study conducted by Engineering and Microbiology of Food Processes, Agro Paris Tech-INRA, France, researchers discovered the fungal-yeast *Yarrowia lipolytica* used in ripening cheese will begin using and converting lactic acid as its main growth factor if essential amino acids are missing. "The consumption of lactate and amino acids is very important for microbial development and/or aroma production during cheese ripening. A strain of *Yarrowia lipolytica* isolated from cheese was grown in a liquid medium containing lactate (lactic acid) in the presence of a low (0.1×) or high (2×) concentration of amino acids. Our results show that

there was a dramatic increase in the growth of *Y. lipolytica* in the medium containing a high amino acid concentration, but there was limited lactate consumption. Conversely, lactate (lactic acid) was efficiently consumed in the medium containing a low concentration of amino acids after amino acid depletion was complete. These data suggest that the amino acids are used by *Y. lipolytica* as a main energy source, whereas lactate (lactic acid) is consumed following amino acid depletion." [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2576680/]

➤ Evidence of the Link Between Increased Lactic Acid Fermentation in the Cell and Cancer

118. In a study conducted by the Department of Hematology and Oncology, University of Regensburg, Germany, researchers found significantly high production of lactic acid in tumors which suppressed immune system T cell function. "A characteristic feature of tumors is high production of lactic acid due to enhanced glycolysis. Here, we show a positive correlation between lactate serum levels and tumor burden in cancer patients and examine the influence of lactic acid on immune functions in vitro. Lactic acid suppressed the proliferation and cytokine production of human cytotoxic T lymphocytes (CTLs) up to 95% and led to a 50% decrease in cytotoxic activity. A 24-hour recovery period in lactic acid-free medium restored CTL [T cell] function. We conclude that high lactic acid concentrations in the tumor environment block lactic acid export in T cells, thereby disturbing their metabolism and function." [http://www.ncbi.nlm.nih.gov/pubmed/17255361]
119. In a study conducted by the Institute of Developmental Biology and Cancer, National Centre for Scientific Research, University of Nice, France, researchers found malignant tumors have high levels of lactic acid due to glucose fermentation (glycolysis) and that blocking the protein that transports lactic acid for use within the tumor significantly suppressed glycolysis, lactic acid utilization and tumor cell growth. "Malignant tumors exhibit increased dependence on glycolysis, resulting in abundant export of lactic acid, a hypothesized key step in tumorigenesis. Lactic acid is mainly transported by two H(+)/lactate symporters, MCT1/MCT4, that require the ancillary protein CD147/Basigin for their functionality. First, we showed that blocking [lactic acid transporter] MCT1/2 in Ras-transformed [tumor] fibroblasts with AR-C155858 suppressed lactate export, glycolysis, and tumor growth. Second, in the human colon adenocarcinoma cell line (LS174T), we showed that combined silencing of [lactic acid transporter] MCT1/MCT4 via inducible shRNA, or silencing of [its required protein] CD147/Basigin alone, significantly reduced glycolytic flux (glucose fermentation) and tumor growth. Collectively, these findings highlight that the major protumoral action of CD147/Basigin is to control the energetics of glycolytic tumors via [lactic acid transporter] MCT1/MCT4 activity and that blocking lactic acid export provides an efficient anticancer strategy." [http://www.ncbi.nlm.nih.gov/pubmed/21930917]
120. In a landmark study conducted by the Department of Stem Cell Biology & Regenerative Medicine, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, researchers found lactic acid stimulated tumor cell metastasis 10-fold. "Here, we directly evaluate whether the end-products of aerobic glycolysis (3-hydroxybutyrate [acid] and L-lactate [lactic acid]) can stimulate tumor growth and metastasis, using MDA-MB-231 breast cancer xenografts as a model system. More specifically, we show that administration of 3-hydroxybutyrate [acid] (a ketone body) increases tumor growth by ~2.5-fold, without any measurable increases in tumor vascularization/angiogenesis. Both 3-hydroxybutyrate [acid] and L-lactate (lactic acid) functioned as chemo-attractants, stimulating the migration of epithelial cancer cells. Although L-lactate (lactic acid) did not increase primary tumor growth, it stimulated the formation of lung metastases by ~10-fold. Thus, we conclude that ketones and lactate (lactic acid) fuel tumor growth and metastasis, providing functional evidence to support the "Reverse Warburg Effect"." [http://www.ncbi.nlm.nih.gov/pubmed/20818174]
121. In a study conducted by the Institute for Clinical Chemistry and Laboratory Medicine, University Hospital of Regensburg, Germany, researchers found blocking the protein CD147 required for MCT1 and MCT4 lactic acid transport and utilization reduced the proliferation of pancreatic cancer cell lines. "MCT1 and MCT4 are the natural transporters of lactate (lactic acid), and MiaPaCa2 [pancreatic cancer] cells exhibited a high rate of lactate (lactic acid) production, which is characteristic for the Warburg effect, an early hallmark of cancer that confers a significant growth advantage. CD147 [protein] is required for the function and expression of the monocarboxylate [lactate] transporters MCT1 and MCT4 that are expressed in human PDAC [pancreatic cancer] cells. Silencing of CD147 [lactic acid transporter protein] by RNA interference (RNAi) reduced the proliferation rate of MiaPaCa2 and Panc1 cells." [http://www.ncbi.nlm.nih.gov/pubmed/19505879]
122. In a study conducted by the Department of Dermatology, Kagoshima University Graduate School of Medical and Dental Sciences, Japan, researchers found blocking the protein CD147 required for MCT1 and MCT4 lactic acid transport and utilization significantly decreased proliferation, invasiveness and production of tumor growth factor VEGF in malignant melanoma cancers. "Cancer cells require glycolysis for energy; this

results in excessive lactate (lactic acid) production and secretion. Lactate, the end product of glycolysis, reduces the extracellular pH and contributes to the proliferation, invasiveness, metastasis, and angiogenesis of tumor cells. Our previous results revealed that the over-expressed CD147/basigin (lactic acid transporter protein) plays a critical role in malignant melanoma (MM) invasiveness, metastasis and angiogenesis. In the present study, we investigated whether CD147/basigin is involved, via its association with MCT1 and 4 to transport lactate, in glycolysis and then contributes to the progression of A375 melanoma cells. A375 cells expressed remarkably higher CD147, MCT1 and 4 and showed increased glycolysis rate compared with normal human melanocytes (NHMC). Furthermore, silencing of CD147/basigin in A375 cells by a siRNA clearly abrogated the expression of [lactic acid transporter] MCT1 and 4 and their co-localization with CD147/basigin and dramatically decreased the glycolysis rate, extracellular pH, and the production of ATP. Thus, cell proliferation, invasiveness, and VEGF production were significantly decreased by siRNA [blocking CD147 lactic acid transporter protein]. These results strongly suggest that highly-expressed CD147 [protein] interacts with [lactic acid transporter] MCT1 and 4 to promote tumor cell glycolysis, resulting in the progression of MM (malignant melanoma)." [<http://www.ncbi.nlm.nih.gov/pubmed/18778892>]

123. In a study conducted by the Dept of Molecular Genetics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan, researchers found lactic acid in tumor cells enhances IL-23 protein production which promotes tumor development. "IL-23 is a proinflammatory cytokine consisting of a p19 subunit and a p40 subunit that is shared with IL-12. IL-23 is overexpressed in and around tumor tissues, where it induces local inflammation and promotes tumor development. Many tumor cells produce large amounts of lactic acid by altering their glucose metabolism. In this study, we show that lactic acid secreted by tumor cells enhances the transcription of IL-23p19 and IL-23 production in monocytes/macrophages and in tumor-infiltrating immune cells that are stimulated with TLR2 & 4 ligands." [<http://www.ncbi.nlm.nih.gov/pubmed/18490716>]
124. In a study conducted by the Department of Hematology and Oncology, University of Regensburg, Germany, researchers found even low concentrations of lactic acid in white blood cells significantly suppressed the tumor necrosis factor (TNF) responsible for: regulation of immune system function, cell death when the cell has mutated beyond repair, and prevention of normal cells mutating into cancer cells. "To study the impact of LA (lactic acid) on TNF secretion, human LPS-stimulated monocytes (white blood cells) were cultured with or without LA (lactic acid). TNF (tumor necrosis factor) secretion was significantly suppressed by [even] low concentrations of LA (lactic acid < or = 10 mM)." [<http://www.ncbi.nlm.nih.gov/pubmed/20026743>]
125. In a study conducted by the Institute of Clinical and Experimental Research, Université catholique de Louvain Belgium, researchers found lactic acid activates HIF-1 via the lactic acid transporter MCT1, which triggers tumor growth in vivo. "The transcription factor hypoxia-inducible factor-1 (HIF-1) is a key contributor to glycolysis (glucose fermentation). We report that lactate (lactic acid), the end-product of glycolysis, inhibits prolylhydroxylase 2 activity and activates HIF-1 in normoxic oxidative (normal oxygen) tumor cells. Lactate (lactic acid) activates HIF-1 and triggers tumor angiogenesis and tumor growth in vivo, an activity that we found to be under the specific upstream control of the lactate (lactic acid) transporter monocarboxylate transporter 1 (MCT1) expressed in tumor cells." [<http://www.ncbi.nlm.nih.gov/pubmed/23082126>]

➤ Evidence of the Link Between Viral-Bacterial-Yeast-Like-Fungus Producing Mycotoxins

126. In a study conducted by the Research Laboratories, Food and Drug Directorate, Department of National Health and Welfare, Canada, researchers found fungus produced specific mycotoxins. "Examination in our laboratory of fungi isolated from foods and feeds for their ability to produce aflatoxins has been expanded to include other mycotoxins. This has been made possible by thin-layer chromatography (TLC) with suitable general solvent systems and only one initial spray reagent. We can thus detect the following toxins: aflatoxins B1, B2, G1, and G2; ochratoxin A; aspertoxin; luteoskyrin; zearalenone; 4-acetamido-4-hydroxy-2-butenic acid  $\gamma$ -lactone; diacetoxyscirpenol and its 8-(3-methyl-butyl)oxy derivative [T-2 toxin]; and nivalenol and its 4-O-acetate, in addition to several antibiotics now regarded as mycotoxins, namely gliotoxin, citrinin, patulin, penicillic acid, and sterigmatocystin. These mycotoxins are produced mainly by [the fungal] species of *Aspergillus*, *Penicillium*, or *Fusarium* but are not necessarily restricted to any one species or genus." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC377058/pdf/applmicro00109-0209.pdf>]
127. In a study conducted by the Botany Department, Faculty of Science, University of Assiut, Egypt, researchers found 11 out of 75 fungal specimens examined were mycotoxigenic, able to produce mycotoxins. "Forty-four fungal species belonging to 20 genera were isolated from 30 samples of qat leaves. The most frequent genera were *Aspergillus*, *Alternaria*, *Penicillium*, and *Cladosporium* followed by *Fusarium*, *Drechslera*, *Chaetomium*, and *Mucor*. The most prevalent species in above genera were *Aspergillus niger*, *A. flavus*, *A.*

fumigatus, *Alternaria alternata*, *Penicillium chrysogenum*, *P. citrinum*, *Cladosporium cladosporioides*, and *Fusarium verticillioides*. From these fungi, 17 species (39%) related to 7 genera (35%) proved to be true endophytes [that being a bacterium or fungus]. Eleven out of 75 isolates were mycotoxigenic. *A. alternata* produced alternariol and alternariol monomethyl ether whereas *A. flavus* produced aflatoxins B1 and B2. Ochratoxin A, sterigmatocystin, citrinin and T-2 toxin were produced by *A. ochraceus*, *A. versicolor*, *P. citrinum* and *F. oxysporum*, respectively. The presence of such toxigenic fungi associated with qat leaves is considered to be a threat to public health." [<http://www.ncbi.nlm.nih.gov/pubmed/11347273>]

128. In a study conducted by the Food Technology Institute - ITAL, Brazil, researchers found many of the fungus present in dried fruit were mycotoxigenic, able to produce mycotoxins. "A total of 117 dried fruit samples (black sultanas, white sultanas, dates, dried plums, dried figs and apricots) from different origins were analysed both for toxigenic fungi and for the presence of [the mycotoxin] ochratoxin A. Amongst the fungi found, *Aspergillus niger* was predominant, with 406 isolates, of which 15% were ochratoxin A producers. They were followed by *A. ochraceus*, with 15 isolates and 87% ochratoxigenics, and *A. carbonarius*, with only five isolates of which 60% were ochratoxin A producers." [<http://www.ncbi.nlm.nih.gov/pubmed/16356890>]
129. In a study conducted by the Dept of Microbiology, Marshall University School of Medicine, Huntington, researchers found evidence that the fungus *Candida albicans* produces the mycotoxin gliotoxin. "Based on the recent finding that *Candida albicans* is able to produce an immunosuppressive mycotoxin, gliotoxin, we analyzed vaginal samples of 3 women severely symptomatic for vaginal candidiasis and found that they contained significant levels of gliotoxin. Three control women who were not colonized with *C. albicans* showed no gliotoxin in vaginal samples." [<http://www.ncbi.nlm.nih.gov/pubmed/7534255>]
130. In a study conducted by the Technical University of Denmark, Department of Systems Biology, Center for Microbial Biotechnology, Denmark, researchers found the fungal mycotoxin sterigmatocystin [associated in stomach cancer with *helicobacter pylori* c. bacteria] is common in many fungal species. "During the last 50 years, the carcinogenic mycotoxin sterigmatocystin (ST) has been reported in several phylogenetically and phenotypically different [fungus] genera: *Aschersonia*, *Aspergillus*, *Bipolaris*, *Botryotrichum*, *Chaetomium*, *Emericella*, *Eurotium*, *Farrowia*, *Fusarium*, *Humicola*, *Moelleriella*, *Monocillium* and *Podospora*. We have reexamined all available strains of the original producers, in addition to ex type and further strains of each species reported to produce [mycotoxin] ST (sterigmatocystin) and the biosynthetically derived aflatoxins. We also screened strains of all available species in *Penicillium* and *Aspergillus* for ST and aflatoxin. Six new [mycotoxin] ST (sterigmatocystin) producing fungi were discovered: *Aspergillus asperescens*, *Aspergillus aureolatus*, *Aspergillus eburneocremeus*, *Aspergillus protuberus*, *Aspergillus tardus*, and *Penicillium inflatum* and one new aflatoxin producer: *Aspergillus togoensis*." [<http://www.ncbi.nlm.nih.gov/pubmed/21530923>]

➤ Evidence of the Link Between Mycotoxins and Cell-Nucleus DNA Damage

131. In a study conducted by the Department of Toxicology, Dalian Medical University, China, researchers found the mycotoxin Patulin produced by the fungus *penicillium* and *aspergillus* significantly induced cell DNA damage. "Patulin (PAT) is a mycotoxin produced by certain species of *Penicillium* and *Aspergillus*. The aim of this study was to assess PAT-induced DNA damage and to clarify the mechanisms, using human hepatoma G2 (HepG2) cells. PAT caused significant increase of DNA migration in single cell gel electrophoresis assay. It was observed that [the mycotoxin] PAT significantly induced DNA damage in GSH-depleted HepG2 cells at lower concentrations. Also, PAT-induced p53 protein accumulation was observed in HepG2 cells, suggesting that the activation of p53 appeared to have been a downstream response to the PAT-induced DNA damage. These results demonstrate that [mycotoxin] PAT (patulin) causes DNA strand breaks in HepG2 cells, probably through oxidative stress." [<http://www.ncbi.nlm.nih.gov/pubmed/19744505>]
132. In a landmark study conducted by the Department of Genetics, Faculty of Medical Sciences, New University of Lisbon, Portugal, researchers confirmed the mycotoxin Patulin causes cell DNA damage which was almost completely prevented with ascorbic acid. "Patulin is a mycotoxin produced by several species of *Penicillium*, *Aspergillus* and *Byssoschlamys* [fungus]. We chose an established model for patulin genotoxicity, i.e. the [DNA] chromosomal aberration assay in V79 Chinese hamster cells, to clarify whether concomitant exposure to ascorbic acid with the mycotoxin [patulin] modulates or not the clastogenicity (DNA chromosomal breakage) of patulin. The results unequivocally show induction of DNA-damaged cells [caused] by [the mycotoxin] patulin as assessed by both cytogenetic assays. In addition, an almost complete abolition of patulin (0.8 microM) clastogenicity [DNA chromosomal damage] was observed in the presence of 80 microM ascorbic acid (vitamin c)." [<http://www.ncbi.nlm.nih.gov/pubmed/10792015>]

133. In a study conducted by the Department of Toxicology, University of Bordeaux 2, France, researchers found a mixture of mycotoxins caused by the fungus *Fusarium* causes cell DNA damage. "We studied the interactive effects of either binary or tertiary mixtures of [fungal] *Fusarium* mycotoxins, [namely] deoxynivalenol (DON), zearalenone (ZEA), and fumonisin B1 (FB1) on the human intestinal cell line, Caco-2, using the endpoints including malonaldehyde (MDA) production, inhibition of protein and DNA syntheses, DNA methylation, DNA fragmentation, and cell viability. The ability of the [myco-] toxins to inhibit DNA synthesis is 45%, 70%, and 43% for 10 microM of ZEA, DON, and FBI, respectively. Altogether, the data indicate that mixtures of *Fusarium* toxins (fungal mycotoxins) are able to induce lipid peroxidation, DNA damage, DNA fragmentation, DNA methylation, and cytotoxicity in Caco-2 cells." [<http://www.ncbi.nlm.nih.gov/pubmed/17109910>]
134. In a study conducted by the Dept of Life Sciences, Chung Shan Medical University, Taiwan, researchers found the mycotoxin Patulin causes cell DNA damage by inducing strand breaks. "Mycotoxins are fungal secondary metabolites with very diversified toxic effects in humans and animals. In the present study, patulin (PAT) and citrinin (CTN), two prevalent mycotoxins, were evaluated for their genotoxic effects and oxidative damage to mammalian cells, including Chinese hamster ovary cells (CHO-K1), human peripheral blood lymphocytes, and human embryonic kidney cells (HEK293). PAT, but not CTN, caused a significant dose-dependent increase in sister chromatid exchange (SCE) frequency in both CHO-K1 and human lymphocytes. PAT also elevated the levels of DNA gap and break in treated CHO-K1 (hamster ovary cells). In the single cell gel electrophoresis (SCGE) assay, exposure of HEK293 (kidney cells) to concentrations above 15 microM of PAT [mycotoxin] induced DNA strand breaks. This suggests that in human cells PAT (patulin mycotoxin) is a potent clastogen with the ability to cause oxidative damage to DNA." [<http://www.ncbi.nlm.nih.gov/pubmed/13678658>]
135. In a study conducted by the Institute for Work Physiology, Dortmund University, Germany, researchers found cells exposed to the mycotoxin Ochratoxin A experienced cell DNA damage in a dose dependent manner. "The mycotoxin ochratoxin A (OTA), a widespread contaminant of food and feedstuffs, is nephrotoxic, immunosuppressive and carcinogenic in domestic and laboratory animals. In this study, the induction of DNA damage by OTA (ochratoxin A) and the subsequent DNA repair was investigated. In Madin-Darby canine kidney (MDCK) cells, [mycotoxin] OTA induced single-strand [DNA] breaks in a concentration dependent manner. A further culture of the damaged cells in the absence of any [OTA] supplement resulted in a complete repair of the DNA damage within 2 hours." [<http://www.ncbi.nlm.nih.gov/pubmed/11876507>]
136. In a groundbreaking study conducted by the Department of Toxicology, University of Würzburg, Germany, rats supplemented with the mycotoxin Ochratoxin A (OTA) for 2 weeks had DNA cell strand breaks compared to control rats. "Ochratoxin A (OTA) is a potent nephrotoxin and renal carcinogen in rats, but the mechanism of OTA tumorigenicity is unknown. In this study, male F344 rats were repeatedly administered [mycotoxin] OTA (0, 250, 500, 1000, and 2000 microg/kg of body wt) or the non-chlorinated analogue ochratoxin B (OTB; 2000 microg/kg of body wt) for 2 weeks (5 days/week), and [cell] DNA breakage was analyzed in target and nontarget tissues using the comet assay. DNA-strand breaks were evident in liver, kidney, and spleen of animals treated with [mycotoxin] OTA (ochratoxin A), and a similar degree of DNA damage was observed in rats treated with OTB, despite the lower toxicity of OTB." [<http://www.ncbi.nlm.nih.gov/pubmed/16097798>]
- Evidence of the Link Between Cell-Nucleus DNA Damage/Mutation/and Inhibition of Tumor Suppressor Genes [specifically p53 and SWI/SNF] and cancer
137. In a landmark study conducted by the Functional Genomics of Ovarian Cancer Laboratory, Cancer Research UK Cambridge Research Institute, researchers found DNA gene mutations in nearly 100% of 123 patients with ovarian cancer in the tumor suppressor gene p53. "High-grade serous (HGS) carcinoma is the most clinically important histological subtype of ovarian cancer. As these tumours may arise from the ovary, Fallopian tube or peritoneum, they are collectively referred to as high-grade pelvic serous carcinoma (HGPC). To identify the true prevalence of TP53 mutations in HGPC, we sequenced exons 2-11 and intron-exon boundaries in tumour DNA from 145 patients. HGPC cases were defined as having histological grade 2 or 3 and FIGO stage III or IV. Surprisingly, pathogenic TP53 [DNA] mutations were identified in 96.7% (n = 119/123) of HGPC cases. Molecular and pathological review of mutation-negative cases showed evidence of p53 dysfunction associated with copy number gain of MDM2 or MDM4, or indicated the exclusion of samples as being low-grade serous tumours or carcinoma of uncertain primary site. Overall, p53 dysfunction rate approached 100% of confirmed HGPCs." [<http://www.ncbi.nlm.nih.gov/pubmed/20229506>]
138. In a study conducted by The Kelly Gynecologic Oncology Service, Department of Gynecology and Obstetrics, and The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins Medical Institutions, Baltimore, Maryland, researchers found DNA gene mutations in over 80% of patients with high grade ovarian cancer in

the tumor suppressor gene p53. "The purpose of this study was to assess the TP53 mutational profile in a relatively large series of high-grade (53 primary and 18 recurrent) and 13 low-grade ovarian serous tumors using DNA isolated from affinity-purified tumor cells and to correlate it with in vitro drug resistance. All samples were affinity purified, and the tumor DNA was analyzed for TP53 mutations in exons 4-9. TP53 [DNA gene] mutations were detected in 57 (80.3%) of 71 high-grade carcinomas and in one (7.8%) of 13 low-grade serous tumors. TP53 mutations were associated with high-grade serous carcinomas and recurrent disease. The frequency of TP53 mutations using purified tumor DNA from ovarian serous carcinomas was 80.3%, which is much higher than previously reported." [<http://www.ncbi.nlm.nih.gov/pubmed/17692090>]

139. In a study conducted by the Cellular Biochemistry and Biophysics Program, Memorial Sloan-Kettering Cancer Center, researchers found the precise mechanism involved in the p53 DNA gene mutation which results in cancer. "Mutations in the p53 tumor suppressor are the most frequently observed genetic alterations in human cancer. The majority of the mutations occur in the core domain which contains the sequence-specific DNA binding activity of the p53 protein, and they result in loss of DNA binding. The core domain structure consists of a beta sandwich that serves as a scaffold for two large loops and a loop-sheet-helix motif. The two loops, which are held together in part by a tetrahedrally coordinated zinc atom, and the loop-sheet-helix motif form the DNA binding surface of p53. The loops and the loop-sheet-helix motif consist of the conserved regions of the core domain and contain the majority of the p53 mutations identified in tumors." [<http://www.ncbi.nlm.nih.gov/pubmed/8023157>]
  140. In a meta-analysis of 24 published studies conducted by the Department of Pathology, Stanford University School of Medicine, California, researchers found SWI/SNF DNA gene mutations widespread across a diverse range of human cancers. "Accumulating evidence suggests that SWI/SNF functions as a tumor suppressor in some cancers. Here, we mined whole-exome sequencing data from 24 published studies representing 669 cases from 18 neoplastic diagnoses. SWI/SNF mutations were widespread across diverse human cancers, with an excess of deleterious mutations, and an overall frequency approaching TP53 mutation. [DNA] mutations occurred most commonly in the SMARCA4 enzymatic subunit, and in subunits thought to confer functional specificity (ARID1A, ARID1B, PBRM1, and ARID2). SWI/SNF mutations were not mutually-exclusive of other mutated cancer genes, including TP53 and EZH2 (both previously linked to SWI/SNF). Our findings implicate SWI/SNF as an important but under-recognized tumor suppressor in diverse human cancers, and provide a key resource to guide future investigations." [<http://www.ncbi.nlm.nih.gov/pubmed/23355908>]
  141. In a study conducted by the Department of Pathology, Stanford University School of Medicine, California, researchers found DNA gene mutations in at least one-third of all pancreatic cancers in the tumor suppressor gene SWI/SNF. "We report here an integrative DNA microarray and sequencing-based analysis of pancreatic cancer genomes. Notable among the alterations newly identified, [include:] genomic [DNA gene] deletions, mutations, and rearrangements [of the] recurrently targeted genes encoding components of the (SWI/SNF) chromatin [tumor suppressor gene] remodeling complex, including all three putative DNA binding subunits (ARID1A, ARID1B, and PBRM1) and both enzymatic subunits (SMARCA2 and SMARCA4). Whereas alterations of each individual SWI/SNF [gene] subunit occurred at modest-frequency, as mutational "hills" in the [DNA] genomic landscape, together they affected at least one-third of all pancreatic cancers, defining SWI/SNF as a major [DNA gene] mutational "mountain"." [<http://www.ncbi.nlm.nih.gov/pubmed/22233809>]
  142. In a study conducted by the Howard Hughes Medical Institute, Chevy Chase, Maryland, researchers found DNA gene mutations in the tumor suppressor gene SWI/SNF occur frequently in human cancers, comparable to that of p53. "We determined mSWI/SNF subunit [DNA gene] mutation frequency in exome and whole-genome sequencing studies of primary human tumors. Notably, mSWI/SNF subunits are mutated in 19.6% of all human tumors reported in 44 studies. In addition, mutations affecting more than one subunit, defined here as compound heterozygosity, are prevalent in certain cancers. Our studies demonstrate that [the] mSWI/SNF [tumor suppressor gene] is the most frequently mutated chromatin-regulatory complex (CRC) in human cancer, exhibiting a broad [DNA gene] mutation pattern, similar to that of [the tumor suppressor gene] TP53." [<http://www.ncbi.nlm.nih.gov/pubmed/23644491>]
- Evidence of the Link Between Inhibition of Tumor Suppressor Genes [specifically p53 and SWI/SNF] Switching Proto-oncogenes to Oncogenes and Cancer
143. In a study conducted by the Department of Biochemistry, St. Jude Children's Research Hospital, Memphis, Tennessee, researchers found DNA mutations in the p53 tumor suppressor gene activates the expression of the oncogene c-Myc. "Mutation of the p53 tumor suppressor gene is the most common genetic alteration in human cancer, and tumors that express mutant p53 may be more aggressive and have a worse prognosis than



p53-null cancers. Here we report mutant p53 can regulate the expression of the endogenous c-myc [onco-] gene and is a potent activator of the c-myc promoter." [http://www.ncbi.nlm.nih.gov/pubmed/9632756]

144. In a study conducted by the Department of Microbiology, Immunology and Cancer Biology, University of Virginia, researchers found DNA mutations of the PTEN tumor suppressor gene subsequently gains control of the mutant p53 tumor suppressor gene to activate the oncogenes c-Myc and Bcl-XL. "Phosphatase [enzyme] and tensin [protein] located on [the DNA] chromosome 10 (collectively known as PTEN) is one of the most frequently mutated tumor suppressors in human cancer including in glioblastoma. Here, we show that PTEN exerts unconventional oncogenic effects in glioblastoma through a novel PTEN/mutant p53/c-Myc/Bcl-XL molecular and functional axis. Using a wide array of molecular, genetic, and functional approaches, we demonstrate that [mutant suppressor gene] PTEN enhances a transcriptional complex containing gain-of-function [of] mutant p53, CBP, and NFY in human glioblastoma [tumor] cells and tumor tissues. The mutant p53/CBP/NFY complex transcriptionally activates the oncogenes c-Myc and Bcl-XL, leading to increased cell proliferation, survival, invasion, and clonogenicity." [http://www.ncbi.nlm.nih.gov/pubmed/23908595]
145. In a study conducted by the Dept of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Brigham and Women's Hospital, Massachusetts, researchers found DNA mutation and inactivation of both tumor suppressor genes p53 and PTEN activates the oncogene c-Myc. "Glioblastoma (GBM) is a highly lethal primary brain cancer with hallmark features of diffuse invasion, intense apoptosis resistance and florid necrosis, robust angiogenesis (tumor growth), and an immature profile with developmental plasticity. In the course of assessing the developmental consequences of central nervous system (CNS)-specific deletion of [tumor suppressor genes] p53 and Pten, we observed a penetrant acute-onset malignant glioma phenotype with striking clinical, pathological, and molecular resemblance to primary GBM [brain cancer] in humans. This primary, as opposed to secondary, GBM [brain cancer] presentation in the mouse prompted genetic analysis of human primary GBM [brain cancer] samples that revealed combined p53 and Pten [DNA tumor suppressor gene] mutations as the most common tumor suppressor defects in primary GBM [brain cancer]. On the mechanistic level, the "multiforme" histopathological presentation and immature differentiation marker profile of the murine tumors motivated transcriptomic promoter-binding element and functional studies of neural stem cells (NSCs), which revealed that dual, but not singular, inactivation of [tumor suppressors] p53 and Pten promotes cellular [oncogene] c-Myc activation. This increased c-Myc activity is associated not only with impaired differentiation, enhanced self-renewal capacity of NSCs, and tumor-initiating cells (TICs), but also with maintenance of TIC tumorigenic potential." [http://www.ncbi.nlm.nih.gov/pubmed/19150964]
146. In a study conducted by the Department of Dermatology and Center for Regenerative Medicine and Stem Cell Biology, University of Colorado Anschutz Medical Campus, researchers found DNA mutations in the p53 tumor suppressor gene activates the expression of the oncogene c-Myc. "We have used two independent microarray platforms to perform a comprehensive and global analysis of tumors arising in a model of metastatic skin cancer progression, which compares the consequences of a GOF (gain-of-function of) p53 mutant [tumor suppressor gene] vs p53 deficiency. DNA profiling revealed a higher level of [DNA] genomic instability in GOF (gain-of-function) vs loss-of-function (LOF) [in] p53 [tumor suppressor gene in] squamous cell carcinomas (SCCs). Moreover, GOF (gain-of-function of) p53 [mutant tumor suppressor gene in] SCCs showed preferential amplification of [the oncogene] Myc with a corresponding increase in its expression and deregulation of Aurora Kinase A." [http://www.ncbi.nlm.nih.gov/pubmed/21963848]
147. In a study conducted by the Department of Molecular Genetics, Albert Einstein College of Medicine, New York, researchers found the tumor suppressor gene SWI/SNF is necessary for activating c-Myc as either a proto-oncogene or oncogene. "The evolutionary conserved SWI/SNF [tumor suppressor gene] complex is one of several multiprotein complexes that activate transcription by remodelling [cell nucleus DNA and protein] chromatin in an ATP-dependant manner. SWI2/SNF2 is an ATPase whose homologues (proteins), BRG1 and hBRM, mediate cell-cycle arrest; the SNF5 homologue (protein), INI1/hSNF5, appears to be a tumour suppressor. A search for INI1-interacting proteins using the two-hybrid system led to the isolation of c-MYC, a [proto-oncogene or oncogene] transactivator. The c-MYC-INI1 [SWI/SNF protein] interaction was observed both in vitro and in vivo. c-MYC-mediated [proto-oncogene or oncogene] transactivation was inhibited by a deletion fragment of [the SWI/SNF protein] INI1 and the ATPase mutant of [protein] BRG1/hSNF2 in a dominant-negative manner. Our results suggest that the SWI/SNF complex is necessary for c-MYC-mediated [proto-oncogene and oncogene] transactivation and that the c-MYC-INI1 [SWI-SNF protein] interaction helps recruit the complex." [http://www.ncbi.nlm.nih.gov/pubmed/10319872]

# The 4<sup>th</sup> Phase of Cancer



Depleted Adrenaline Depletes Dopamine and Tryptophan Levels Resulting in Niacin Deficiency, Breaking (Krebs) Citric Acid Cycle

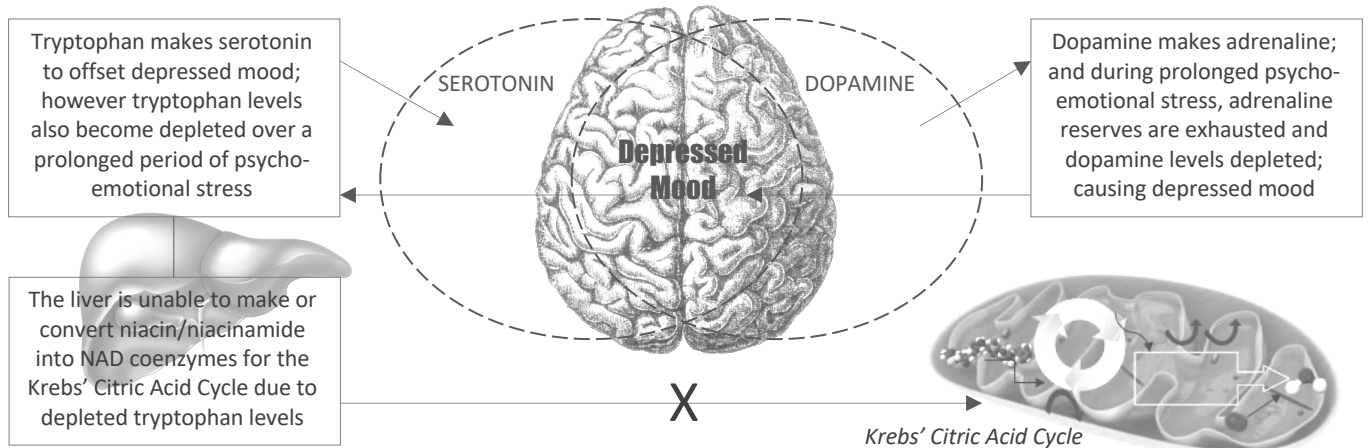
Phase

4

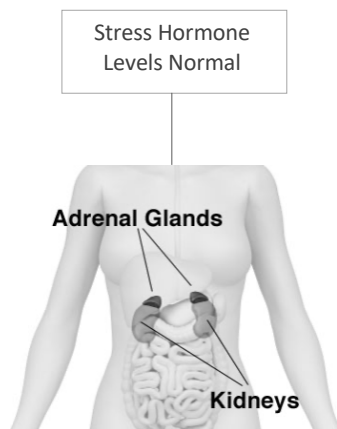
During phase 4, depleted adrenaline (epinephrine) levels cause a depletion of dopamine in the brain. Adrenaline is made by dopamine, and as more and more dopamine is used up during stress, the amino-acid tryptophan creates serotonin to offset depressed mood. This subsequently results in a depletion of tryptophan which is needed to synthesize niacin/niacinamide (vitamin B3) for cell respiration. Niacin/niacinamide is converted by tryptophan into NAD coenzymes which are subsequently used by the Krebs' Citric Acid Cycle in the mitochondria of the cell for glucose conversion, cell respiration and creation of ATP energy. Without tryptophan and niacin/niacinamide, the Krebs's Citric Acid Cycle / Oxidative Phosphorylation metabolic pathway is broken.

## The Theory

In the 1950's, Dr Abram Hoffer, Director of Research at the Regina Psychiatric Services Branch, Department of Public Health, Saskatchewan, Canada, while administering high doses of oral vitamin c and niacin (vitamin B3) to patients hospitalized with psychiatric disorders, accidentally found this treatment of vitamin c and niacin also effected a cure in a number of psychiatric patients who had incurable cancer. Dr Hoffer subsequently went on to treat cancer patients in his own private practice from 1967 to 2005 and found the principle treatment of vitamin c and niacin in late stage cancer patients, whether undertaking chemotherapy, radiation or not, resulted in a life extension increase from 5.7 months to 100 months on average. Dr Hoffer was particularly focused on the health properties of niacin—and for good reason—for niacin is crucial to the Krebs' Citric Acid Cycle, and in turn to the optimal functioning of the metabolic pathway Oxidative Phosphorylation. Niacin and niacinamide (also known as nicotinamide) are both forms of vitamin B3 and are synthesized from the amino acid tryptophan in the liver into coenzymes called NAD for the Krebs's Citric Acid Cycle to convert glucose into ATP energy for the cell and for the body. If this critical glucose-converting-ATP-energy-producing factory is shut down, then the cell is forced to ferment rising glucose levels via the process known as glycolysis to obtain reduced amounts of ATP energy. This in turn creates a highly acidic low pH environment and the somatid pleomorphises (changes) within the body into viral-bacterial-yeast-like-fungus to ferment the excess glucose within cells, causing normal cells to mutate into cancer cells during the diving process. In cancer patients we see a chronic niacin deficiency caused by a chronic tryptophan deficiency. It takes 60mg of tryptophan for the liver to synthesize 1mg of niacin in the body, and when tryptophan is depleted so too is niacin. Tryptophan becomes depleted in the body when an individual experiences prolonged psycho-emotional stress, as a result of the stress depleting all-important adrenaline reserves. Adrenaline is made by dopamine, and as more and more dopamine is used up during stress, the amino-acid tryptophan synthesizes serotonin to offset depressed mood. This subsequently results in a depletion of serotonin and tryptophan, meaning niacin and niacinamide cannot be created or converted by tryptophan into NAD coenzymes for the Krebs' Citric Acid Cycle for healthy cell functioning.



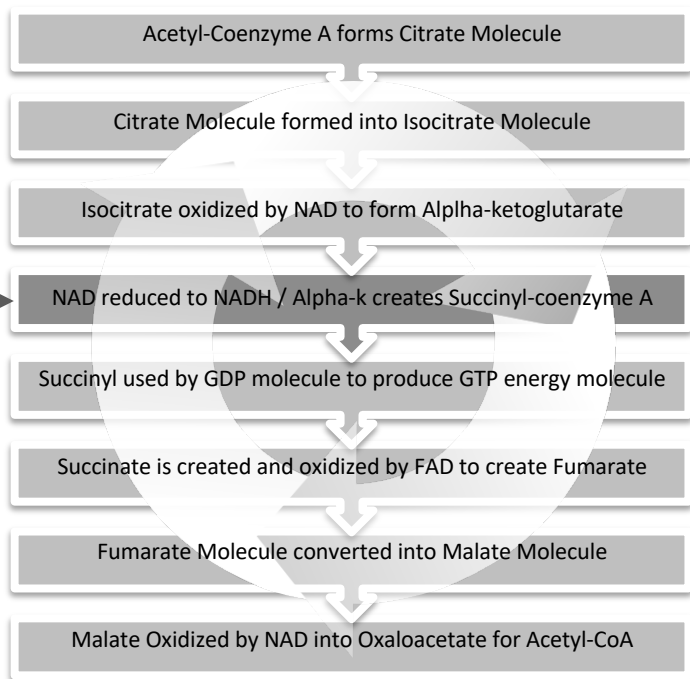
**Krebs' Citric Acid Cycle of the Cancer-Free Individual**



Stress Hormone Levels Normal

Adrenaline Levels Normal

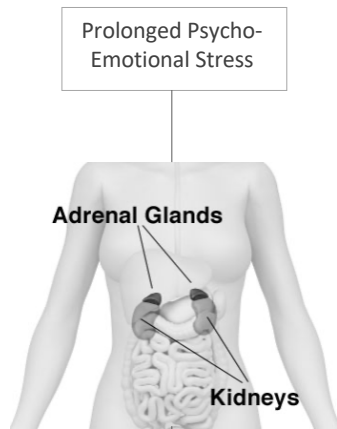
The Liver synthesizes and converts Niacin and Niacinamide into NAD using amino acid Tryptophan



ATP energy is created from GTP energy molecules, NADH and Succinate within the metabolic pathway known as *Oxidative Phosphorylation*

**Glucose is converted by Krebs' Citric Acid Cycle into ATP energy for the Cell and the Body**

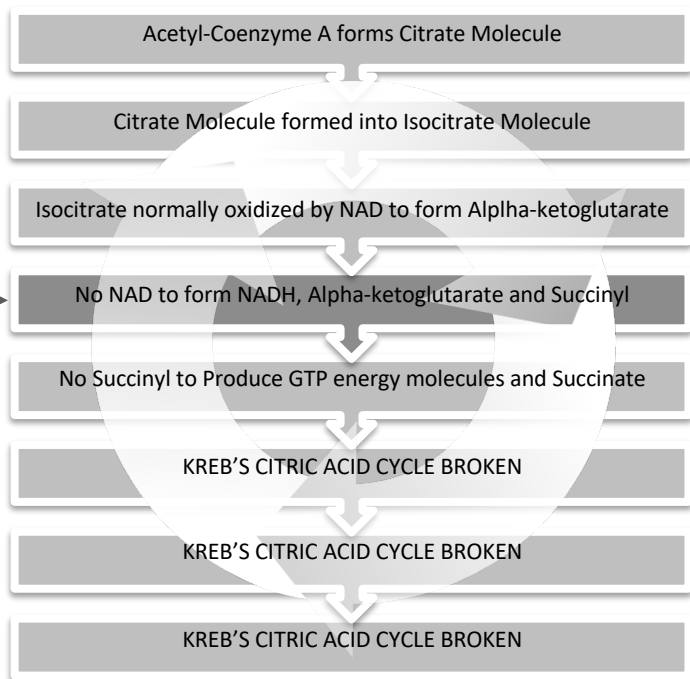
**Krebs' Citric Acid Cycle of the Individual with Cancer**



Prolonged Psycho-Emotional Stress

Adrenaline Levels Depleted

The Liver unable to synthesize and convert Niacin / Niacinamide into NAD due to depleted Tryptophan



ATP energy unable to be created via Krebs' Citric Acid Cycle for *Oxidative Phosphorylation* due to absent GTP energy molecules, NADH and Succinate

**Krebs' Citric Acid Cycle unable to convert Glucose into ATP energy; the Cell Ferments Glucose Instead**

Dr Abram Hoffer [Clinical Procedures in Treating Terminally Ill Cancer Patients with Vitamin C + Niacin]: "I recall that in 1952 when I was working as a resident in psychiatry at the Munroe Wing which was a part of the General Hospital in Regina, a woman who had her breast removed for cancer was admitted to our ward. She was psychotic. This poor lady had developed a huge ulcerated lesion, she wasn't healing, and she was in a toxic delirium. Her psychiatrist decided that he would give her shock treatment, which was the only treatment available at that time. I decided I would like to give her vitamin C instead. As director of research, I had the option of going to the physicians and asking them if I could do this with their patients. A friend of mine was her doctor and he said, "Yes, you can have her." He said, "I'll withhold shock treatment for three days." I had thought that I would give her three grams per day, which was our usual dose at that time, for a period of weeks, but when he told me I could have three days only, I decided that this would not do. Therefore, I decided to give her one gram every hour. I instructed the nurses that she was to be given a gram per hour except when she was sleeping. When she awakened, she would get the vitamin C that she had missed. We started her on a Saturday morning and when her doctor came back on Monday morning to start shock treatment she was mentally normal. I wanted to know, if vitamin C would have any therapeutic effect. To our amazement her lesion on her breast began to heal. She was discharged, mentally well, still having cancer and she died six months later from her cancer. This was an interesting observation which I had made at that time and which I had never forgotten.

There was another root to this interest. In 1959, we found that the majority of schizophrenic patients excreted in their urine a factor that we call the mauve factor, which we have since identified as kryptopyrrole. I was looking for a good source of this urinary factor. We had thought that the majority of schizophrenics had it. We thought that normal people did not have it but I was interested in determining how many people who were stressed also had the factor. Therefore, I ran a study of patients from the University Hospital who were on the physical wards. They had all sorts of physical conditions including cancer, I found to my amazement that half the people with lung cancer also excreted the same factor. By 1960, a very famous gentleman of Saskatchewan, one of the professors retired and was admitted to the psychiatric department at our hospital. He was psychotic. He had been diagnosed as having a bronchiogenic carcinoma. It had been biopsied and was visualized in the x-ray and it had also been seen in the bronchoscope. While they were deciding what to do, he became psychotic so they concluded that he had secondaries in his brain. Because he became psychotic, he was no longer operable and instead they gave him cobalt radiation. It didn't help the psychosis any. He was admitted to our ward where he stayed for about two months, completely psychotic. He was placed on the terminal list, I discovered that he was on our ward, so I thought he may have some mauve factor in his urine. On analysis he revealed huge quantities.

I had discovered by then that if we gave large amounts of B3 (Niacin) along with vitamin C to these patients, regardless of their diagnosis, they tended to do very well. He was started on three grams per day each of nicotinic acid (niacin) and ascorbic acid on a Friday. On Monday he was found to be normal. A few days later I said to him, "You understand that you have cancer?" He said, "Yes, I know that." He was friendly with me because I had treated his wife for alcoholism some time before. I said to him, "If you will agree to take these two vitamins as long as you live, I will provide them for you at no charge. In 1960, I was the only doctor in Canada that had access to large quantities of vitamin C and niacin. They were distributed through our hospital dispensary. He agreed. That meant he had to come to my office every month in order to pick up two bottles of vitamins. I didn't know that it might help his cancer. I was interested only in his psychological state. However, to my amazement he didn't die. After 12 months, I was having lunch with the director of the cancer clinic, a friend of mine, and I said to him, "What do you think about this man?" And he said, "We can't understand it, we

can't see the tumor any more." I thought he'd say, "Well, isn't that great." So I asked, "Well, what's your reaction?" He responded, "We are beginning to think we made the wrong diagnosis." The patient died, 30 months after I first saw him, of a coronary. Here's another case that is very interesting. A couple of years later, a mother I had treated for depression came back to see me. Once more she was depressed. She said she had a daughter 16, who had just been diagnosed as having an osteogenic sarcoma of the arm. Her surgeon had recommended that the arm be amputated. She was very depressed over this and so I asked her, "Do you think you can persuade your surgeon not to amputate the arm right away?" And I told her the story about the man with the lung cancer. She brought her daughter in and I started her on niacinamide, 3 grams per day, plus vitamin C, three grams per day. She made a complete recovery and is still well, not having had to have surgery. But this time I concluded that maybe B-3 (niacin) was the therapeutic factor. The reason for that, of course, is very simple. I liked B3 and I didn't have much interest in vitamin C.

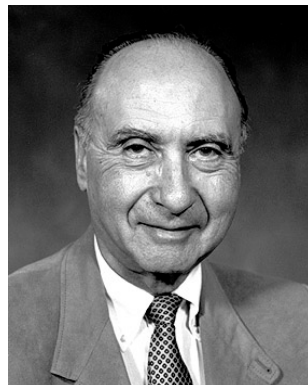
When I moved to Victoria, another strange event happened. In 1979, a woman developed jaundice and during surgery a six centimeter in diameter lump in the head of the pancreas was found. They were too frightened to do a biopsy, which apparently is quite standard. They thought that the biopsy might disseminate the tumor. The surgeon closed and told her to write her will. They said she might have three to six months at the most. She was a very tough lady and she had read Norman Cousins' book *Anatomy of an Illness*. So she said to her doctor, "To hell with that, I'm not going to die." And she began to take vitamin C on her own, 12 grams per day. When her doctor discovered what she was doing, he asked her to come and see me, because by that time I was identified as a doctor who liked to work with vitamins. I started her on 40 grams of vitamin C per day, to which I added niacin, zinc and a multi-vitamin, multimineral preparation. I had her change her diet by staying away from high protein and fat. I didn't hear from her again for about six months. One Sunday, she called me. Normally when I get a call from a patient on a Sunday, it's bad news. She immediately said, "Dr. Hoffer, good news! I asked, "What's happened?" She said, "They have just done a CT scan and they can't see the tumor," So then she said, "They couldn't believe it. They thought the machine had gone wrong; so they did it all over again. And it was also negative the second time." She had her last CT scan in 1984, no mass, and she is still alive and well today.

The last case I'm going to give details of one born in 1908. His mother died of cancer and his father had a coronary at the age of 80. My patient had had a myocardial infarction in 1969, and again in 1977, followed by a coronary bypass. In March of 1978, he suddenly developed pain in his left groin and down the left leg. In February 1979, he developed a bulge in his left groin, and later, severe pain with movement. In surgery, a large mass infiltrating sarcoma was found, part of which was removed, but a mass the size of a grapefruit was left. The tumor was eroding into a ramus of the pubic bone. They concluded that it was not radiosensitive. In March he had palliative radiation to his left half - 4500 rads. The pain was gone at the end of the radiation. On May 28, he developed a severe staph infection, and in June he was very depressed because his wife was dying of cancer and also he was suffering from drainage of chronic infection. In July he still had a purulent discharge in two areas. Now the mass was visible and palpable in the left iliac area above the inguinal ligaments. In January of 1980, he saw me for the first time. I started him on 12 grams of vitamin C per day and I recommended to his referring doctor that he give him IV ascorbic acid, 2.5 grams, twice per week, which he agreed to. I gave him niacin, vitamin B6 and zinc to balance it out. In April, the mass began to regress and the oncologist wrote, "This is interesting, it must be something else." In other words, the patient said, the vitamin C is helping and the oncologist said, no it isn't. The oncologist put a note in the file, "He's probably responding to chemotherapy." But he had never had chemotherapy. The infection was gone. In May 1980, his x-ray showed reconstruction of the left superior pubic ramus. In July he wrote to me telling how

grateful he was to be so well. In February of 1988, he went back to the cancer clinic for some recurrent facial skin carcinoma. He died in the fall of 1989 of coronary disease when he was 81. This man survived 10 years after having been diagnosed with cancer.

I examined every cancer patient referred to me between July 1978 and April 1988 and followed them to January 1990. I did not miss a single case. A total of 134 were seen. And I dated the time that they first saw me as day zero. The only thing I wanted to look at was survival. I wanted hard data, something that couldn't be argued with. I wasn't going to say the patients were better or not better because these are subjective terms. These 134 fell into two groups. It wasn't my fault that this happened because I treated every one of them exactly the same way. I did not plan a double blind prospective study. What I planned and what I did was to advise every patient what I thought they ought to do in terms of their cancer. If they were getting radiation, I suggested they stay with it. If they were getting chemotherapy, I suggested they stay with that. I never advised them about their surgery, chemotherapy or radiation. However, out of these 134, there were 33 who did not or could not follow the program. For example, on chemotherapy, they were so nauseated that they couldn't hold anything down and if they couldn't hold the vitamins down they weren't going to do very much good. There were some who didn't believe in the program.

The other 101 did stay on their program at least two months. Some went off in the third or fourth month but they stayed on it for at least two months. I was encouraged by Linus Pauling. I followed them all. First of all, I contacted their doctors. I contacted the patients that were still alive. I contacted their families. I got all their records from the cancer clinics. I had a complete file on every patient I had seen so that I knew within a matter of months exactly what had happened to them. The results were analyzed by Dr. Linus Pauling using a new technique for analyzing cohorts. The data is as follows: 33 controls - they survived an average of 5.7 months, from the first day that I saw them. There were two treatment cohorts: a cohort of 40 females with cancer of the breast, ovary, uterus or cervix. The second cohort of 61 were other types of cancer. The cohorts were divided into two groups. First were the poor responders, those who didn't do well; they survived an average of 10 months, nearly twice as long as the control. The others, the good responders, were divided into two groups. The female group survived an average of 122 months and the other group 72 months. I think this is very significant. There was a tremendous difference in the survival rate. Today, all the controls are dead, 50% of the treated group are still alive. Over the past year, I did another survey and of the remainder only three more have died. It cannot be all due to cancer because I'm dealing with a population with ages between 60 and 80. They are going to die of other causes as well. This was published in the *Journal of Orthomolecular Medicine*, Volume 5, p. 143, 1990.



[Dr Abram Hoffer, PhD, 1917-2009]

Dr Abram Hoffer [Clinical Procedures in Treating Terminally Ill Cancer Patients with Vitamin C + Niacin] – The Treatment Protocol: “The first thing I try to do is to cut their fat way down. So, I put them all on a dairy free program. I reduce, but I don't eliminate, meat and fish, and I ask them to increase their vegetables, especially raw, as much as they can. I think it's a good, reasonable diet, which most people can follow without too much difficulty. Having spent some time with them going over what they ought to eat, I begin to talk about the nutrients. The first one, of course, is vitamin C. The dose is variable. I find that most patients can take 12 grams per day without much difficulty, that's the crystallin vitamin C sodium ascorbate or calcium ascorbate. They take one teaspoon three times per day. If they do not develop diarrhea, I ask them to increase it until this occurs and then to cut back below that level. I think in many cases it would be desirable to use intravenous vitamin C and there are doctors now in Canada doing that. I also add vitamin B-3, either niacin or niacinamide. I prescribe from 500 mg to 1500 mg per day. Before I did that empirically, now there is a lot of evidence that B3 does have pretty interesting anticancer properties. Two years ago, in Texas at one of the osteopathic colleges, there was an international congress, Vitamin B-3 and Cancer. There is a lot of work being done in this area today. I also add a B (vitamin) complex preparation 50 or 100. I think vitamin E is an extremely important antioxidant and I use that as well, 800 to 1200 I. U. They also get 25,000 to 75,000 units of beta carotene. I sometimes use vitamin A. I like to use folic acid for lung cancer, and for cancer of the uterus because of work that has been done showing that folic acid might reverse a positive pap smear to negative. I use selenium, 200 mcg, three times per day. I use some zinc, especially for prostatic cancers and I do use calcium-magnesium preparations. ”

Dr Abram Hoffer founded the International Society for Orthomolecular Medicine and his above cancer treatment protocol was endorsed by founding father of vitamin c therapy, Linus Pauling who stated: “For many years Dr. Hoffer has prescribed for his psychiatric patients large amounts of vitamin C, usually 12 grams per day, a good amount of niacin, 1.5 or 3 grams per day, and mega-amounts of several other vitamins and certain minerals. Those patients with various kinds of cancer who followed his regimen, in addition, for some of them, to receiving conventional therapy, have survived far longer, on the average about 16 times as long, years rather than months. I now recommend strongly that cancer patients follow the regimen prescribed by Dr. Hoffer, rather than just taking megadoses of vitamin c.”

Within the 4<sup>th</sup> Phase of Cancer the following sequence of events can be observed in the cancer patient:



## The Evidence

The evidence for Phase 4 of Cancer can be broken down into the following components: a) the link between chronic stress and depleted dopamine levels, b) the link between depleted dopamine levels and a reactionary increase and net depletion of serotonin, c) the link between depleted [serotonin-producing] tryptophan levels and depression, d) the link between depleted tryptophan levels and cancer, e) the link between depleted tryptophan levels and niacin / niacinamide deficiency, f) the link between niacin / niacinamide deficiency and depleted dopamine and serotonin levels, g) the link between niacin / niacinamide deficiency and reduced production of [Kreb's Citric Acid Cycle] NAD coenzymes, h) the link between cancer and niacin / niacinamide / NAD coenzyme deficiency.

### ➤ Evidence of the Link Between Chronic Stress and Depleted Dopamine Levels

148. In a study conducted by the Institute of Psychobiology and Psychopharmacology, National Research and Advisory Department Italy, researchers found mice exposed to inescapable shock had depleted dopamine levels compared to mice exposed to escapable shock. "It has been previously shown that rodents exposed to stressful experiences show a biphasic (two phase) response of the mesolimbic dopamine (DA) system, that is, initial increase of DA (dopamine) release followed by a decrease below control levels. Evidence is now presented showing that mice exposed to a series of foot shocks show an increase of DA (dopamine) release in the nucleus accumbens septi (NAS) if they are allowed to control the shock experience (shocked condition) and a decrease of DA (dopamine) release in this brain area if they are not allowed to exert any control (yoked condition)." [<http://www.ncbi.nlm.nih.gov/pubmed/8182476>]
149. In a further study conducted by the Institute of Psychobiology and Psychopharmacology, National Research and Advisory Department Italy, researchers confirmed inescapable shock depletes brain dopamine levels and freedom from shock stimuli restores dopamine levels. "Exposure to either restraint or footshock (3-60 min) induced similar biphasic alterations of [dopamine metabolite] 3-methoxytyramine concentrations in the [brain] nucleus accumbens septi (NAS) of mice; [that being an initial increase, followed by a decrease below control levels]. These data suggest biphasic alteration of DA (dopamine) release during prolonged stress exposure. The analysis of release in restrained conscious rats by in vivo microdialysis (10-240 min) showed a similar biphasic DA (dopamine) evolution (initial increase followed by decrease below baseline levels) in the [brain] NAS. Moreover, freed rats showed an immediate increase of DA (dopamine) release over baseline levels. Taken together, these results support the hypothesis that biphasic alteration of DA (dopamine) transmission in the mesolimbic [brain] system is a general response to stress and suggest that the initial increase of DA (dopamine) release represents an arousal response while the subsequent decrease in DA (dopamine) release may be related to coping failure." [<http://www.ncbi.nlm.nih.gov/pubmed/1933302>]
150. In a study conducted by the Laboratory of Endocrinology, Rockefeller University, New York, researchers found rats exposed to chronic social stress had depleted brain dopamine levels. "The visible burrow system (VBS) is a chronic social stress paradigm in which a dominance hierarchy forms among male rats housed with females. Behavior in the VBS (visible burrow system) was observed and rats were classified as dominants or subordinates. Subordinates were further sub-classified on the basis of stress hormone response to an acute stressor (i.e. restraint stress). Decreased dopamine transporter density was detected after single VBS [chronic social stress] exposure in the [brain] dorsolateral caudate putamen of NRS (non-responsive subordinates) and after repeated VBS [chronic social stress] exposure in the Acb [brain region] of NRS [rats] compared with controls. These results suggest that long-term changes in dopamine activity in mesolimbic [brain] structures persist after repeated exposures to chronic social stress." [<http://www.ncbi.nlm.nih.gov/pubmed/14980394>]
151. In a study conducted by the Department of Neuroscience, University of Pittsburgh, researchers found rats exposed to chronic prolonged unavoidable stress had a 64% reduction in the number of active dopamine cells. "In this study, the effects of a chronic stressor (prolonged exposure to cold) on the spontaneous activity of DA (dopamine) neurons in the [brain] ventral tegmental area and medial substantia nigra (VTA/mSN) were examined. Extracellular single-unit recordings of DA (dopamine) neurons were performed in rats following a 17-day continuous exposure to a cold (4 degrees C) environment. Compared to controls, cold-exposed rats displayed 64% fewer spontaneously active DA (dopamine) neurons. These results show that chronic stress can lead to the cessation of spontaneous activity in a subpopulation of VTA/mSN [brain] DA (dopamine) cells. These changes may indicate that unlike acute stress, which can potently activate the [brain] mesolimbic /mesocortical DA (dopamine) systems, chronic stress leads to an adaptive reduction in the number of active DA (dopamine) cells." [<http://www.ncbi.nlm.nih.gov/pubmed/11182536>]



152. In a study conducted by the Department of Neuroscience, University of Siena, Italy, researchers found brain dopamine levels decreased in rats exposed to chronic unavoidable stress. "As the activity of the neuronal dopamine (DA) transporter (DAT) is considered to be a critical mechanism for determining the extent of DA (dopamine) receptor activation, we investigated whether a 3-week exposure to unavoidable stress, which produces a reduction in DA (dopamine) output in the [brain] nucleus accumbens shell (NAcS) and medial prefrontal cortex (mPFC), would affect DAT (dopamine transporter) density and DA D1 (dopamine) receptor complex activity. Rats exposed to unavoidable stress showed a decreased DA (dopamine) output in the [brain] NAcS accompanied by a decrease in the number of DAT (dopamine transporter) binding sites, and an increase in the number of DA D1 (dopamine) binding sites and Vmax of SKF 38393-stimulated adenylyl cyclase. In the [brain] mPFC, stress exposure produced a decrease in DA (dopamine) output. This study shows that exposure to a chronic unavoidable stress that produces a decrease in DA (dopamine) output in fronto-mesolimbic [brain] areas induced several adaptive neurochemical modifications selectively in the [brain] nucleus accumbens." [<http://www.ncbi.nlm.nih.gov/pubmed/12421362>]
153. In a landmark study of combat veterans conducted by the Division of Molecular Medicine, Rudjer Boskovic Institute, Croatia, researchers found combat veterans with chronic post traumatic stress disorder (PTSD) had significantly lower dopamine activity. "The aim of the study was to determine plasma dopamine beta-hydroxylase (DBH) activity and [dopamine] DBH-1021C/T gene polymorphism (changes) in combat veterans with (N = 133) or without (N = 34) chronic PTSD (post traumatic stress disorder). War veterans with PTSD had lower DBH (dopamine beta-hydroxylase) activity, associated with the DBH-1021C/T variant in [dopamine] DBH genes, than veterans without PTSD. A significantly lower plasma DBH (dopamine beta-hydroxylase) activity was found in combat veterans with PTSD carrying the CC genotype as compared to veterans without PTSD carrying the corresponding genotype." [<http://www.ncbi.nlm.nih.gov/pubmed/17853400>]
154. In a study conducted by the German Primate Center, Division of Neurobiology, Germany, researchers found tree shrews exposed to chronic psycho-social stress for 28 days experienced reduced dopamine activity. "In the present study, the animals were subjected to psychosocial stress for 28 days. Brain dopamine transporter binding sites were quantified by in vitro autoradiography using [3H] WIN 35,428 as ligand. Chronic stress reduced the number of [dopamine] binding sites (Bmax) in the caudate nucleus and the putamen [of the brain] without affecting the affinity (Kd). The present study shows that a naturalistic stressor, such as chronic psychosocial conflict, decreases dopamine transporter binding sites in motor-related brain areas, suggesting that the reduction in locomotor activity in subordinate tree shrews is related to the downregulation of dopamine transporter binding sites." [<http://www.ncbi.nlm.nih.gov/pubmed/10762338>]
155. In a study conducted by the Pharmacology Department, Tsumura and Company, Japan, researchers found rats exposed to prolonged chronic stress had marked reduction in dopamine transmission. "We have previously reported that chronic stress administered by water immersion and restraint for 4 weeks induces an organic disorder such as [brain] hippocampal neuronal degeneration. We therefore examined whether chronically stressed (4 weeks) and recovered (for 10 days) rats show (exhibit) a working memory impairment caused by reduced dopamine (DA) transmission in the [brain] PFC (pre-frontal cortex), as suspected in the neuro-psychiatric disorders. The stress impaired the spatial working memory evaluated by T-maze task and induced a marked reduction of DA (dopamine) transmission [naturally] concomitant with an increase in DA D1 (dopamine) receptor density in the [brain] PFC." [<http://www.ncbi.nlm.nih.gov/pubmed/10662846/>]

➤ Evidence of the Link Between Depleted Dopamine Levels and a Reactionary Increase/ Net Depletion of Serotonin

156. In a study conducted by the Department of Anatomy and Cell Biology, Wayne State University School of Medicine, Michigan, researchers found 60 days after induced dopamine depletion in rats, serotonin levels doubled. "Sixty days after bilateral dopamine (DA) depletion (>98%) with 6-hydroxydopamine (6-OHDA) in neonatal rats, serotonin (5-HT) content doubled and (serotonin) 5-HT(2A) receptor mRNA expression rose 54% within the [brain] rostral striatum." [<http://www.ncbi.nlm.nih.gov/pubmed/10446352>]
157. In a study conducted by the Department of Neurology, Georgetown University Hospital, Washington, DC, researchers found 6 weeks after induced dopamine depletion in rats, serotonin turnover increased by 90% which resulted in a net depletion of serotonin of more than 50%. "In order to evaluate the influence of dopaminergic transmission on regional brain utilization of serotonin (5HT), the effects of the destruction of the ascending dopamine (DA) pathways on regional brain (serotonin) 5HT metabolism in the rat were examined. Complete unilateral lesions of the nigrostriatal DA (brain dopamine) pathways (> [resulting in a 90% DA [dopamine] loss) were made by infusing the neurotoxin 6-hydroxy-dopamine into either the left medial forebrain bundle (MFB) or the left substantia nigra (SN). At 6 weeks after the lesions, levels of 5HT

(serotonin) and its major metabolite, 5-hydroxyindoleacetic acid (5HIAA), were determined bilaterally in the striatum, frontal cortex, and hypothalamus [of the brain]. In the striatum of the lesioned hemisphere, the 5HT (serotonin) level decreased by more than 50%, while the ratio of 5HIAA:5HT (an index of 5HT serotonin turnover) increased by more than 90%. These results suggest that the loss of DA (dopamine) innervation in the [brain] striatum triggers an increase in 5HT (serotonin) turnover and a net depletion of 5HT (serotonin) in the striatum." [http://www.ncbi.nlm.nih.gov/pubmed/7512513]

158. In a study conducted by the Department of Pharmacology & Toxicology, Northwest Center for Medical Education, Indiana University School of Medicine, researchers found the suppression of dopamine by the dopamine inhibitor GBR resulted in increased serotonin turnover. "Repeated administration of GBR (20 mg/kg/day) for 2 or 4 days decreased DA (dopamine) and DOPAC; only the 4-day regimen decreased 5HT (net serotonin) and increased 5HIAA (serotonin metabolite) levels. The results suggest GBR decreases the steady-state levels of DA (dopamine), resulting in a compensatory increase in the turnover of 5HT (serotonin) that is dependent on the presence of intact dopaminergic terminals. Thus, the effect of GBR on 5HT (serotonin) turnover is indirect. The studies provide further support for a prominent dopaminergic influence on [brain] striatal 5HT (serotonin) metabolism." [http://www.ncbi.nlm.nih.gov/pubmed/7540709]
159. In a study conducted by the Neuroregeneration Laboratories, McLean Hospital, Harvard Medical School, Massachusetts, researchers found 5 weeks after induced dopamine depletion in rats, serotonin levels increased significantly. "In this animal model for Parkinson's disease (PD), the effect of destroying ascending DA (dopamine) pathways on extracellular levels of serotonin (5-HT) and 5-HT innervation in rat [brain] striatum were examined. At 5 weeks after [brain dopamine] lesioning, extracellular levels of DA (dopamine) and 5-HT (serotonin) were determined with microdialysis and high-pressure liquid chromatography under basal conditions. 6-OHDA (brain dopamine) lesioning reduced extracellular levels of DA (dopamine) below detection limits and led to statistically significant increases in extracellular 5-HT (serotonin)." [http://www.ncbi.nlm.nih.gov/pubmed/12831863]

➤ Evidence of the Link Between Depleted [Serotonin-Producing] Tryptophan Levels and Depression

160. In a landmark study conducted by the MRC Unit of Clinical Pharmacology, Littlemore Hospital, Oxford, UK, researchers found tryptophan levels were significantly lower in patients with major depression. "Plasma total tryptophan (TRP) concentration was significantly lower in 31 patients with major depression compared to a healthy control group. The ratio of plasma TRP (tryptophan) concentration to that of other branch chain amino acids (the TRP:BCAA ratio) was also decreased. Further analysis revealed that the decrease in plasma TRP (tryptophan) and TRP:BCAA ratio was most apparent in patients with major depression and melancholia. Our data suggest that in some depressed patients, reductions in plasma tryptophan availability may contribute to abnormalities in brain 5-hydroxytryptamine (serotonin) function." [http://www.ncbi.nlm.nih.gov/pubmed/2148339]
161. In a further study conducted by the MRC Unit of Clinical Pharmacology, Littlemore Hospital, Oxford, UK, researchers found recovered depressed patients who drank a mixture that reduced tryptophan levels by 75% caused the return of depressive symptoms in two-thirds of patients. "We studied 15 women who had suffered recurrent episodes of major depression but had recovered and were no longer on drug treatment. Patients received two amino acid mixtures in a double-blind crossover design. One of the mixtures was nutritionally balanced and contained tryptophan, and the other was identical except it contained no tryptophan. Participants were scored on the Hamilton rating scale for depression (HAMD) before and 7 h [hours] after drinking each mixture. The tryptophan-free mixture produced a 75% reduction in plasma tryptophan concentration. After drinking the tryptophan-free mixture, ten of the 15 women experienced temporary but clinically significant depressive symptoms." [http://www.ncbi.nlm.nih.gov/pubmed/9093253]
162. In a study conducted by the Neuroimmunology Research Group, School of Medicine & Trinity College Institute of Neuroscience, Ireland, researchers found patients with major depressive disorder had reduced circulating tryptophan levels compared to matched controls. "Here we examined circulating concentrations of inflammatory cytokines, and the acute phase protein CRP alongside plasma tryptophan, kynurenine, kynurenic acid and (tryptophan metabolite) 3-hydroxyanthranilic acid (3-HAA) concentrations...in patients with major depressive disorder (MDD) compared with age and sex-matched controls. A depletion in tryptophan was evident in depressed patients and was correlated with HAM-D scores. These data support the idea that a mild inflammatory signature is evident in MDD (major depressive disorder) and is accompanied by reduced circulating tryptophan concentrations." [http://www.ncbi.nlm.nih.gov/pubmed/22683764]

163. In a study conducted by the NYU Child Study Center, Child and Adolescent Psychiatry, New York University School of Medicine, researchers found tryptophan levels were significantly decreased in adolescents with melancholic major depressive disorder compared to non-melancholic depressive and control subjects. "This study addresses this issue by examining whether adolescent MDD (major depressive disorder) with and without melancholic features (M-MDD and NonM-MDD) have distinct biological features in the kynurenine pathway (KP). The KP (kynurenine pathway) is initiated by pro-inflammatory cytokines via induction of the enzyme indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan (TRP) into kynurenine (KYN). KYN is further metabolized into neurotoxins linked to neuronal dysfunction in MDD (major depressive disorder). Subjects were 20 adolescents with M-MDD, 30 adolescents with NonM-MDD, and 22 healthy adolescents. As hypothesized, compared to healthy controls, adolescents with M-MDD (melancholic major depressive disorder) had significantly decreased plasma TRP (tryptophan) levels ( $718.59 \pm 727.12$  ng/ml versus  $982.87 \pm 406.31$  ng/ml,  $t = 2.34$ ,  $df = 65$ ;  $p = .02$ ). As predicted, relative to adolescents with NonM-MDD (non-melancholic major depressive disorder), adolescents with M-MDD (melancholic major depressive disorder) had significantly decreased plasma TRP (tryptophan) levels ( $718.59 \pm 727.12$  ng/ml versus  $1022.77 \pm 643.03$  ng/ml,  $t = -2.81$ ,  $df = 63$ ;  $p = .006$ )." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3711227/>]
164. In a study conducted by the Department of Psychiatry, University Hospitals of Cleveland, Ohio, researchers found tryptophan levels were significantly lower in major depressed patients compared with healthy controls. "The authors have measured the following in depressed patients and normal control subjects: plasma levels of L-TRP (tryptophan), and the competing amino acids valine, leucine, isoleucine, tyrosine, and phenylalanine, together with indices of immune function. Both plasma levels of L-TRP (tryptophan) and the L-TRP/CAA (tryptophan/competing amino acids) ratio were significantly lower in major depressed subjects as compared with healthy control subjects." [<http://www.ncbi.nlm.nih.gov/pubmed/7908745>]
165. In a study conducted by the Clarke Division, Centre for Addiction and Mental Health, Toronto, researchers found patients with major depressive disorder receiving treatment of tryptophan resulted in a significantly greater decrease in depression. "Randomized, double-blind, placebo-controlled trial: thirty individuals with major depressive disorder. Treatment over 8 weeks with 20 mg of fluoxetine per day and either tryptophan (2 to 4 g per day) or placebo. During the first week of treatment, there was a significantly greater decrease in HDRS-29 depression scores, and a similar trend in BDI scores, in the tryptophan/fluoxetine group than in the placebo/fluoxetine group." [<http://www.ncbi.nlm.nih.gov/pubmed/11022398>]

➤ Evidence of the Link Between Depleted Tryptophan Levels and Cancer

166. In a study conducted by the Department of Internal Medicine, Hamamatsu University School of Medicine, Japan, researchers found tryptophan levels were significantly lower in lung cancer patients compared to healthy controls. "Indoleamine 2,3-dioxygenase (IDO) catalyzes the rate-limiting step of tryptophan (Trp) degradation along the kynurenine (Kyn) pathway. By depleting tryptophan, IDO is considered to be a fundamental immune escape mechanism for tumor cells. The concentrations of Trp (tryptophan) and Kyn were measured in the sera of 123 patients with lung cancer and 45 healthy controls. Trp (tryptophan) concentrations were significantly lower in patients with lung cancer than in healthy controls ( $62.6 \pm 15.8$  microM vs.  $71.1 \pm 11.8$  microM, respectively). The IDO (tryptophan depleting) activity determined by the Kyn/Trp ratio was significantly higher in the patients than in the controls ( $47.1 \pm 21.3$  vs.  $32.9 \pm 9.10$ , respectively). In addition, patients in the advanced stages of lung cancer had significantly lower Trp (tryptophan) concentrations and higher IDO (tryptophan depleting) activity than those in the early stages." [<http://www.ncbi.nlm.nih.gov/pubmed/19487045>]
167. In a leading study conducted by the Department of Internal Medicine, Medical University, Innsbruck, Austria, researchers found lung cancer patients had reduced tryptophan levels compared to healthy controls and found an association between reduced tryptophan levels, cancer and fatigue [known to be caused by adrenal depletion]. "Patients with cancer often suffer from fatigue and decreased quality of life which might be related to the breakdown of essential amino acid tryptophan. In 50 patients with lung cancer we examined fatigue and the deterioration of quality of life. Results were compared with tryptophan breakdown as well as serum concentrations of immune activation markers. The mean tryptophan concentration in patients was  $53.4 \pm 2.3$   $\mu$ mol/L (mean  $\pm$  S.E.M.), mean kynurenine concentration was  $2.4 \pm 1$   $\mu$ mol/L and the mean Kyn/Trp was  $52.3 \pm 6.0$   $\mu$ mol/mmol. In comparison to the ranges observed in healthy controls, the cancer patients presented with lower tryptophan and higher kynurenine levels, and accordingly with increased Kyn/Trp. Conclusions: Tryptophan breakdown relates with fatigue and impaired quality of life in patients with lung cancer." [<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0036956>]

168. In a further study conducted by the Division of Biological Chemistry, Biocenter, Innsbruck Medical University, Austria, researchers found decreased tryptophan levels in patients with various cancers which were further decreased with progression of disease. "Venous blood was collected from 146 patients with gastrointestinal tumors (n = 43), hematological malignancy (n = 40), gynecological neoplasms (n = 26), lung cancer (n = 20) and from tumors of other localization (n = 17). Serum tryptophan concentrations were lower in patients with progressive disease, and decreased tryptophan concentrations were related to decreased QoL (quality of life) and increased fatigue. Concentrations of tryptophan and kynurenine and the kynurenine to tryptophan ratio were predictive for impaired QoL (quality of life) and increased fatigue in univariate regression analysis." [<http://www.ncbi.nlm.nih.gov/pubmed/17356858>]
169. In a study conducted by the Department of Toxicology, Gazi University, Turkey, researchers found depleted tryptophan levels in patients with small and non-small lung cancer compared with healthy controls. "We examined serum tryptophan and kynurenine concentrations in nine patients with small cell lung cancer and in 27 patients with non-small cell lung cancer. Compared with controls, patients presented with lower tryptophan concentrations and with higher serum kynurenine to tryptophan ratios, an index of tryptophan degradation. We conclude that in the majority of patients with non-small cell lung cancer and small cell lung cancer, enhanced tryptophan degradation can be observed. The capacity of the tumour to escape normal host immune defence may be influenced by tryptophan degradation. Results of this pilot study deserve further confirmation." [<http://www.ncbi.nlm.nih.gov/pubmed/19702697>]
170. In a study conducted by the Dept. of Gynecologic Oncology, University of Groningen, The Netherlands, researchers found patients with ovarian, vulvar and endometrial cancer have depleted tryptophan levels. "Concentrations of tryptophan and kynurenine were determined in pretreatment serum samples of patients with endometrial (n = 41), ovarian (n = 28), and vulvar cancer (n = 40) and compared to 19 healthy female controls. Patients with endometrial, ovarian, and vulvar cancer have increased tryptophan degradation compared to controls resulting in higher serum kynurenine concentrations and a higher kyn/trp (kynurenine / tryptophan) ratio." [<http://www.ncbi.nlm.nih.gov/pubmed/21720257>]
171. In a landmark study conducted by the Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, and Department of Physiology, Anatomy and Genetics, University of Oxford, United Kingdom, researchers found a direct correlation between tryptophan depletion, immune suppression and tumor cell growth. "Previous work has shown that tryptophan depletion to concentrations 10 mM reduces T cell proliferation, whereas at 1 mM, T cell proliferation is completely inhibited. We confirmed using an in vitro model that depletion of tryptophan by IDO+ tumor cells inhibited T cell proliferation, and that replacement of fresh tryptophan or inhibition of IDO was sufficient to restore proliferation to normal levels. These findings highlight the ability of IDO-expressing tumor cells to thrive in a tryptophan-depleted microenvironment by expressing a novel, highly tryptophan-specific transporter, which is resistant to inhibition by most other amino acids." [<http://www.jimmunol.org/content/early/2011/07/08/jimmunol.1000815.full.pdf>]

➤ Evidence of the Link Between Depleted Tryptophan Levels and Niacin / Niacinamide Deficiency

172. In a study conducted by the Dept of Human Health Science, Faculty of Human Sciences, Osaka International University for Women, Japan, researchers found depleted tryptophan levels resulted in lower conversion of tryptophan to niacin. "We investigated the effects of feeding various types of nicotinic acid-free, tryptophan-limiting diets on the conversion ratio of tryptophan to niacin in rats. Various tryptophan-limiting diets were made by adding zein, gelatin, glycine, threonine, methionine, or glycine + threonine + methionine to a nicotinic acid-free, 9% casein diet. When the rats were fed with the tryptophan-limiting diets, the conversion ratio of tryptophan to niacin was markedly decreased. However, the ratio recovered after the addition of tryptophan to the tryptophan-limiting diets. These results clearly prove that the conversion was lowest when the rats were fed with the tryptophan-limiting diets." [<http://www.ncbi.nlm.nih.gov/pubmed/8987665>]
173. In a landmark study conducted by the Laboratories of Food Science and Nutrition, School of Human Cultures, The University of Shiga Prefecture, Japan, researchers determined the precise amount of tryptophan needed to synthesize niacin in the human liver. "In order to establish the human requirements of niacin, it is first important to know how much tryptophan is converted to niacin in the human body. In general, 60 mg of tryptophan is equivalent to 1 mg of niacin, whereas the conversion ratio of tryptophan to niacin is yet to be confirmed. The aim of this study was to know the conversion ratio of tryptophan to niacin in Japanese females fed a purified diet, which followed the Japanese Dietary Reference Intakes. Ten young Japanese females were housed in the same facility and given the same daily living activity schedule for 7 d [days]. The diet was niacin free. Tryptophan-niacin metabolites in the urine were measured and the conversion ratio of

tryptophan to niacin calculated. It was calculated that if the excretory percentage of niacin metabolites in the urine were 60%, of the tryptophan ingested, the conversion factor would be a value of 67, meaning that is 67 mg of tryptophan is equal to 1 mg of niacin." [<http://www.ncbi.nlm.nih.gov/pubmed/15895512>]

174. In a study conducted by the Department of Medicine, Brigham and Women's Hospital, Harvard University, Boston, Massachusetts, researchers found niacin therapy restores depleted tryptophan levels. "Decreased plasma tryptophan in persons infected with human immunodeficiency virus (HIV) was first reported over a decade ago, and this observation has since been confirmed by many groups. Starting with the hypothesis that HIV induces a [niacin deficient] pellagra-like state and that plasma tryptophan in HIV-infected patients is decreased as a known biochemical correlate of pellagra, we predicted that niacin therapy would reverse plasma tryptophan depletion as it does in pellagra. After receiving approval from the institutional review board, we treated HIV-infected patients for 2 months with high-dose niacin in the form of oral nicotinamide. There was an average 40% increase in plasma tryptophan in the four HIV-infected individuals who completed the 2-mo [month] protocol." [<http://www.ncbi.nlm.nih.gov/pubmed/11448590>]
175. In a study conducted by the Department of Biochemistry, University College, London, researchers found the incubation of rat liver cells with tryptophan synthesized high levels of niacin. "Incubation of hepatocytes (liver cells) with tryptophan also resulted in the formation and release from the cells of a considerable amount of niacin, as well as the two principal metabolites of NAD(P), N1-methyl nicotinamide and methyl pyridone carboxamide. It is suggested that, in the liver, performed niacin is not utilized for nucleotide synthesis, and indeed the function of the liver appears to be synthesis of niacin from tryptophan, and its release for use by extrahepatic (non-liver) tissues that lack the pathway for de novo (renewed) synthesis of nicotinamide nucleotides from tryptophan." [<http://www.ncbi.nlm.nih.gov/pubmed/2965917>]
176. In a study conducted by the Courtauld Institute of Biochemistry, Middlesex Hospital, London, researchers found rats fed a high dietary intake of tryptophan led to a considerable increase in niacin metabolites. "The metabolic fate of high dietary intakes of nicotinamide, nicotinic acid and tryptophan, and of acute doses of nicotinamide and nicotinic acid, has been studied in the rat. A high dietary intake of tryptophan (5.9 g/kg diet) led to a considerable increase in liver NAD(P) and also in urinary excretion of niacin metabolites." [<http://www.ncbi.nlm.nih.gov/pubmed/2960374>]

➤ Evidence of the Link Between Niacin / Niacinamide Deficiency and Depleted Dopamine and Serotonin Levels

177. In a landmark study conducted by the Palladin Institute of Biochemistry, NAS of Ukraine, researchers found niacin / niacinamide restored serotonin and dopamine levels in patients with Parkinson's disease. "It was established, that serotonin and dopamine content and dopamine uptake by brain nerve endings under experimental parkinsonism are decreased. Nicotinamide (niacinamide, NAm) nicotinoyl-GABA (niacin + chief inhibitory neuro-transmitter GABA) administration leads to normalization of these parameters. It was shown that NAm (niacinamide) was more effective on serotonin content while nicotinoyl-GABA (niacin + GABA) on dopamine one. Thus, NAm (niacinamide), nicotinoyl-GABA (niacin + GABA) and NAD are involved in the regulation of brain neurotransmission under experimental parkinsonism and can be useful in treatment of Parkinson's disease." [<http://www.ncbi.nlm.nih.gov/pubmed/12199067>]
178. In a further study conducted by the Palladin Institute of Biochemistry, NAS of Ukraine, researchers found niacinamide restored serotonin levels in diabetic rats to normal levels. "Studies of neurotransmitter uptake and release by isolated rats brain cortex synaptosomes demonstrated that serotonin uptake was by 41% lower in streptozotocin-diabetic rats as compared to control. Nicotinamide (Nam, Niacinamide) administration (200 mg/kg body weight daily, 14 days) to diabetic rats restored synaptosomal serotonin uptake up to control levels. Data obtained confirm the important role of NAm (Niacinamide) in the pathogenesis of diabetic encephalopathies [brain disorders]." [<http://www.ncbi.nlm.nih.gov/pubmed/8588246>]
179. In a study conducted by the Institute of Undersea and Hyperbaric Medicine, Taiwan, researchers found the pretreatment of rats with niacinamide reduced the effect of induced dopamine depletion. "The present study examined the effects of nicotinamide (niacinamide) on the D-amphetamine (AMPH)-induced dopamine (DA) depletion and energy metabolism change in the rat [brain] striatum. In chronic studies, co-administration of AMPH with desipramine, a drug that retards the metabolism of AMPH, caused a significant decrease of striatal DA (dopamine) content measured 7 days later. Pretreatment with nicotinamide (niacinamide) (500 mg/kg, i.p.), the precursor molecule for the electron carrier molecule nicotinamide adenine dinucleotide (NAD), attenuated (reduced) this effect of AMPH." [<http://www.ncbi.nlm.nih.gov/pubmed/10566977>]

180. In a study conducted by the Graduate Institute of Life Sciences, National Defense Medical Center, Taiwan, researchers found the pretreatment of rats with niacinamide reduced the effect of induced brain dopamine depletion. "The aim of the present study was to examine the effects of nicotinamide (niacinamide), a co-factor in the electron transport chain, on the relationship between methamphetamine (MA)-induced striatal [brain] dopamine (DA) depletion and energy metabolism change. Four injections of MA at 2 hour intervals resulted in decreases of 51% and 23%, respectively, in striatal DA (dopamine) and adenosine 5'-triphosphate (ATP) levels 5 days later. Nicotinamide (niacinamide) (500 mg/kg, i.p.) treatment prior to each MA injection attenuated (reduced) the reductions of [brain] striatal DA (dopamine) and ATP contents." [<http://www.ncbi.nlm.nih.gov/pubmed/9223070>]
181. In a landmark study conducted by the Department of Neurosurgery, Zhejiang University School of Medicine, China, researchers found pretreatment with niacinamide protected against induced depletion of dopamine causing Parkinson's disease. "Parkinson's disease was induced by injection of MPTP in adult male C57BL/6 mice, [while] nicotinamide (niacinamide) (500 mg/kg,i.p.) was given prior to subacute MPTP administration. Nicotinamide (niacinamide) administration resulted in [the] sparing [of] striatal [brain] dopamine levels from MPTP-induced dopamine depletion. Nicotinamide (niacinamide) protects dopaminergic neurons against MPTP-induced neurodegeneration, which suggests that the neuroprotective effects be associated with the inhibition of cell injuries and NOS activities." [<http://www.ncbi.nlm.nih.gov/pubmed/22499510>]

➤ Evidence of the Link Between Niacin / Niacinamide Deficiency and Reduced Production of NAD Coenzymes

182. In a study conducted by the School of Public Health, University of California, Los Angeles, researchers found niacin deficient rats had reduced NAD coenzyme levels resulting in cell DNA damage. "The niacin cofactor, NAD, is the [underlying] substrate for poly(ADP-ribose) polymerase, an enzyme associated with DNA repair. We investigated, therefore, whether hepatic (liver enzyme) poly(ADP-ribose) polymerase activity was altered and DNA strand breaks in lymphocytes and liver were greater in niacin-deficient rats. A niacin deficiency was established in weanling rats with diets containing 1.5 mg/kg of niacin. Based on lower growth rates and NAD concentrations in blood, liver and skeletal muscle, this diet maintained rats in a deficient state for 1 month, and, when the dietary niacin was reduced to 0.5 mg/kg, rats remained deficient for an additional month. The hepatic poly(ADP-ribose) polymerase activity was decreased in one experiment when mean hepatic (liver) NAD concentrations were 0.60 and 0.51 mumol/g at d 34 and d 60, respectively, compared with 0.77 and 0.80 mumol/g in [niacin] pair-fed controls. Exposure to this system caused more DNA strand breaks in [cell] lymphocytes and hepatic (liver) nuclei from niacin-deficient rats compared with the same tissues from controls. The results suggest that, in rats, although hepatic (liver enzyme) poly(ADP-ribose) polymerase activity can be elevated, a severe niacin deficiency may increase the susceptibility of DNA to oxidative damage, likely due to a lower availability of NAD." [<http://www.ncbi.nlm.nih.gov/pubmed/8336204>]
183. In a study conducted by the Department of Nutritional Sciences, College of Biological Sciences, University of Guelph, Canada, researchers found niacin deficient rats resulted in decreased NAD coenzyme levels. "In this study we have measured lung tissue NAD<sup>+</sup> and poly(ADP-ribose) concentrations in response to hyperoxia (excessive oxygen) and niacin deficiency in rats. Male weaning rats consumed niacin-deficient (ND) or niacin-replete pair-fed (PF) diets for 7 days. Rats from each diet group (n = 6) were then housed in normobaric 85% (excessive) oxygen for 5 days. Normoxic (normal oxygen) controls were maintained in air. Niacin deficiency decreased lung NAD<sup>+</sup> in normoxic (normal oxygen) rats, but surprisingly, this deficit was partially reversed by hyperoxia (excessive oxygen)." [<http://www.ncbi.nlm.nih.gov/pubmed/8728036>]
184. In a further study conducted by the Dept of Nutritional Sciences, University of Guelph, Canada, researchers found rats fed niacin and niacinamide resulted in a significant increase in NAD coenzyme levels. "In our first study, using rats, 2 wk of dietary nicotinic acid (niacin) supplementation (500 and 1000 mg/kg diet) caused elevated levels of NAD<sup>+</sup> in the blood, liver, heart and kidney, while nicotinamide (niacinamide) caused elevated levels only in the blood and liver, compared with controls fed a [low niacin] diet containing 30 mg/kg nicotinic acid. Both nicotinic acid (niacin) and nicotinamide (niacinamide), at 1000 mg/kg diet, caused elevations in liver NAD<sup>+</sup>, by 44 and 43%, respectively. Following treatment with the hepatocarcinogen (liver cancer)-(inducing compound) diethylnitrosamine, higher levels of hepatic (liver) NAD<sup>+</sup> were observed in rats fed both nicotinic acid (niacin) and nicotinamide (niacinamide) at 1000 mg/kg diet." [<http://www.ncbi.nlm.nih.gov/pubmed/7782898>]
185. In a final study conducted by the Dept of Human Biology and Nutritional Sciences, University of Guelph, Canada, researchers found niacin deficiency significantly reduces NAD coenzyme levels in the bone marrow of rats. "Rats were fed [reduced niacin] diets containing 0 or 30 mg/kg of added niacin for a period of 2-3 wk.

Niacin deficiency (ND) alone caused a significant depression in nucleated red blood cells (30%). ND (niacin deficiency) alone caused an 80% decrease in bone marrow NAD<sup>+</sup> levels at all time points." [http://www.ncbi.nlm.nih.gov/pubmed/12791512]

➤ Evidence of the Link Between Cancer and Niacin / Niacinamide / NAD Coenzyme Deficiency

186. In a study conducted by the Department of Applied Biological Science, Tokyo Noko University, researchers found niacin inhibited the invasion of liver cancer cells. "The effects of niacin, namely, nicotinic acid (niacin) and nicotinamide (niacinamide), and (niacin alkaloid) trigonelline on the proliferation and invasion of cancer cells were studied using a rat ascites hepatoma (liver cancer) cell line of AH109A in culture. Niacin and (niacin alkaloid) trigonelline inhibited the invasion of hepatoma (liver cancer) cells at concentrations of 2.5-40 microM without affecting proliferation. Hepatoma (liver cancer) cells previously cultured with a reactive oxygen species (ROS)-generating system showed increased invasive activity. Niacin and [niacin] trigonelline suppressed this ROS-potentiated invasive capacity through simultaneous treatment of AH109A cells with the ROS-generating system. The present study indicates for the first time the anti-invasive activities of niacin and (niacin alkaloid) trigonelline against cancer cells." [http://www.ncbi.nlm.nih.gov/pubmed/15785001]
187. In a study conducted by the Arizona Cancer Center, Department of Radiation Oncology, University of Arizona College of Medicine, researchers found niacin significantly reduced the incidence of skin cancer in mice exposed to UV radiation. "Dietary supplementation with 0.1%, 0.5%, or 1.0% niacin reduced the control incidence of skin cancer from 68% to 60%, 48%, and 28%, respectively, at 26.5 weeks after the first UV treatment. Niacin supplementation elevated skin NAD content, which is known to modulate the function of DNA strand scission surveillance proteins p53 and poly(ADP-ribose) polymerase, two proteins critical in cellular responses to UV-induced DNA damage." [http://www.ncbi.nlm.nih.gov/pubmed/10453439]
188. In a study conducted by the Department of Human Health and Nutritional Sciences, University of Guelph, Canada, researchers found niacin deficient rats had much higher rates of cancer. "Niacin deficiency impairs poly(ADP-ribose) formation and enhances ethylnitrosourea (ENU)-induced carcinogenesis. Rats were fed niacin deficient (ND), pair-fed (PF) control (30 mg nicotinic acid/kg), or pharmacological niacin (NA; 4 g nicotinic acid/kg) diets. After 2 wk, rats were gavaged (administered) every other day with [cancer-inducing] ENU. Total cancers developed more rapidly in rats on the ND (niacin deficient) diet compared to those receiving high dose supplements of NA (niacin). Importantly, all of these differences occurred in the leukemias, especially the nonlymphocytic leukemia fraction with incidences of 36%, 17%, and 11% in ND (niacin deficient), PF (control), and NA (niacin) rats, respectively." [http://www.ncbi.nlm.nih.gov/pubmed/18444158]
189. In a landmark study conducted by the Department of Medical Biochemistry, University of Madras, Taramani Campus, and Department of Medical Oncology, Government Royapettah Hospital, India, researchers found the addition of niacin, coenzyme Q10 and riboflavin in cancer therapy resulted in significantly lower tumor cell markers. "In breast cancer patients, it is not the primary tumour, but its metastases at distant sites that are the main cause of death. Circulating breast cancer tumour markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) are reliable indicators of impending relapse, in which an increasing tumour marker level is associated with a very likelihood of developing recurrence. In the present study, 84 breast cancer patients were randomized to receive a daily supplement of 100 mg coenzyme Q10 (CoQ10), 10 mg riboflavin and 50 mg niacin (CoRN) one dosage per day along with 10 mg tamoxifen (TAM) twice a day. Serum CEA and CA 15-3 levels were elevated in untreated breast cancer patients (group II) and their tumour marker levels significantly reduced upon tamoxifen therapy for more than 1 year (group III). Group III patients [after 1 year subsequently] supplemented with CoRN (niacin, coenzyme Q10, riboflavin) for 45 days (group IV) and 90 days (group V) along with tamoxifen significantly reduced CEA and CA 15-3 levels [even further]. This study suggests supplementing CoRN (niacin, coenzyme Q10, riboflavin) to breast cancer patients along with tamoxifen reduces the serum tumour marker level and thereby reduces the risk of cancer recurrence and metastases." [http://www.ncbi.nlm.nih.gov/pubmed/17268082]
190. In a further study conducted by the Department of Medical Biochemistry, University of Madras, Taramani Campus, India, researchers found the Krebs' Citric Acid Cycle / metabolic pathway Oxidative Phosphorylation of rats with breast cancer supplemented with niacin, coenzyme Q10 and riboflavin was restored. "Rats were selected for the experimental study. Mammary carcinoma was induced by the oral administration of 7,12-dimethylbenz[a]anthracene, and treatment was started by the oral administration of the energy-modulating vitamins riboflavin (45 mg/kg body weight per d), niacin (100 mg/kg body weight per d) and coenzyme Q10 (40 mg/kg body weight per d) for 28 days. Mitochondria were isolated from the mammary gland and liver of

all four groups, and the Krebs cycle and oxidative phosphorylation enzymes were assayed. In mammary carcinoma-bearing animals, the activities of the Krebs cycle and oxidative phosphorylation enzymes were significantly decreased. These activities were restored to a greater extent in animals treated with energy-modulating [riboflavin, niacin and coenzyme Q10] vitamins. From these experimental results, one may hypothesize that the combination therapy of energy-modulating vitamins could be of major therapeutic value in breast cancer." [<http://www.ncbi.nlm.nih.gov/pubmed/16022760>]

191. In a study conducted by the Department of Molecular and Experimental Medicine, The Scripps Research Institute, California, researchers found reduction of NAD coenzyme levels increased tumor cell metastasis. "Despite advances in clinical therapy, metastasis remains the leading cause of death in breast cancer patients. Mutations in mitochondrial DNA, including those affecting complex I and oxidative phosphorylation, are found in breast tumors and could facilitate metastasis. This study identifies mitochondrial complex I as critical for defining an aggressive phenotype in breast cancer cells. Specific enhancement of mitochondrial complex I activity inhibited tumor growth and metastasis through regulation of the tumor cell NAD<sup>+</sup>/NADH redox balance, mTORC1 activity, and autophagy. Conversely, nonlethal reduction of NAD<sup>+</sup> levels by interfering with nicotinamide phosphoribosyltransferase expression rendered tumor cells more aggressive and increased metastasis. The results translate into a new therapeutic strategy: enhancement of the NAD<sup>+</sup>/NADH balance through treatment with NAD<sup>+</sup> precursors inhibited metastasis in xenograft models, increased animal survival, and strongly interfered with oncogene-driven breast cancer progression in the MMTV-PyMT mouse model. Thus, aberration in mitochondrial complex I NADH dehydrogenase activity can profoundly enhance the aggressiveness of human breast cancer cells, while therapeutic normalization of the NAD<sup>+</sup>/NADH balance can inhibit metastasis and prevent disease progression." [<http://www.ncbi.nlm.nih.gov/pubmed/23426180>]
192. In a leading study by the Department of Medicine, University of Alabama at Birmingham, researchers found that NAD<sup>+</sup> enzyme 15-hydroxyprostaglandin dehydrogenase (15-PDGH) significantly decreased migration and proliferation of cancer cells in vitro and in vivo. "It has been shown that expression of NAD(+) linked 15-hydroxyprostaglandin dehydrogenase (15-PGDH), a key enzyme responsible for PGE(2) (prostaglandin) inactivation, is suppressed in the majority of cancers, including breast and colon carcinoma. The purpose of this study was to investigate cytotoxicity in vitro and therapeutic efficacy in vivo of (NAD<sup>+</sup> linked) 15-PGDH-mediated cancer therapy. The in vitro study showed that Ad-mediated (NAD<sup>+</sup>) 15-PGDH expression significantly decreased proliferation and migration of cancer cells. Animal breast and colon tumor therapy studies showed that (NAD<sup>+</sup>) 15-PGDH gene therapy produced a significant delay in 2LMP and LS174T tumor growth. Combined therapy using (NAD<sup>+</sup>) 15-PGDH and anti-VEGF antibody (bevacizumab) significantly increased inhibition of growth of LS174T tumor xenografts in comparison with agents alone." [<http://www.ncbi.nlm.nih.gov/pubmed/19887544>]
193. In a study conducted by the Dept of General Surgery, Weill Cornell Medical College, New York, researchers found NAD<sup>+</sup> enzyme 15-hydroxyprostaglandin dehydrogenase (15-PDGH) was significantly decreased in non-small lung cancer cells. "Elevated levels of procarcinogenic prostaglandins (PG) are found in a variety of human malignancies including non-small cell lung cancer (NSCLC). NAD<sup>+</sup>-dependent (enzyme) 15-hydroxyprostaglandin dehydrogenase (15-PGDH), the key enzyme responsible for metabolic inactivation of PGs (prostaglandins), is down-regulated in various malignancies. The main objective of this study was to elucidate the effect of loss of (NAD<sup>+</sup>) 15-PGDH on levels of bioactive lipids in NSCLC (non-small cell lung cancer). We found that levels of cyclooxygenase-2 and microsomal prostaglandin synthase 1 were commonly increased whereas the amount of (NAD<sup>+</sup>) 15-PGDH was frequently decreased in NSCLC compared with adjacent normal lung. Reduced expression of (NAD<sup>+</sup>) 15-PGDH occurred in tumor cells and was paralleled by decreased (NAD<sup>+</sup>) 15-PGDH activity in tumors." [<http://www.ncbi.nlm.nih.gov/pubmed/19138967>]
194. In a study conducted by the Dept of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, researchers found mice injected with NAD + enzyme 15-hydroxyprostaglandin dehydrogenase (15-PDGH) had a significant decrease in tumor cell growth. "To further explore if (NAD<sup>+</sup>) 15-PGDH is related to tumorigenesis, athymic (T-cell deficient) nude mice were injected with control A549 [tumor] cells or cells transiently over-expressing [normal] wild-type or mutant (NAD<sup>+</sup>) 15-PGDH. It was found that mice injected with control A549 [tumor] cells or with cells expressing mutant (NAD<sup>+</sup> 15-PGDH) enzyme produced tumors normally. However, mice injected with A549 [tumor] cells expressing wild-type [naturally occurring NAD<sup>+</sup>] 15-PGDH had a significant decrease in tumor growth. Examining the effects of (NAD<sup>+</sup>) 15-PGDH expression on cellular changes in A549 [tumor] cells, we found that over-expression of (NAD<sup>+</sup>) 15-PGDH induced apoptosis (cell death) of A549 [tumor] cells as evidenced by fragmentation of DNA. These results suggest that (NAD<sup>+</sup>) 15-PGDH may decrease the level of proliferative PGE2 (prostaglandin), induce apoptosis (tumor cell death) and function like a tumor suppressor." [<http://www.ncbi.nlm.nih.gov/pubmed/15358636>]



# The 5<sup>th</sup> Phase of Cancer

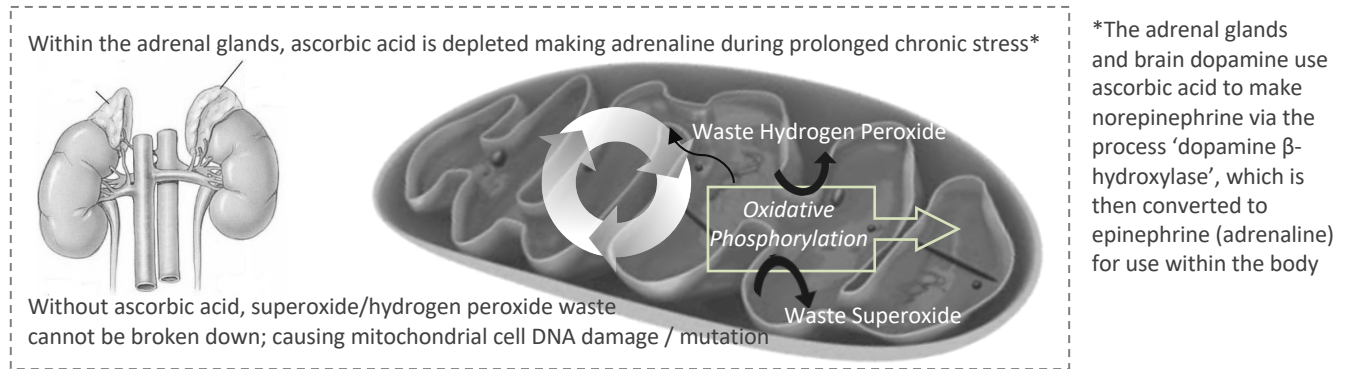


## Phase

Depleted Adrenaline and High Stress Cortisol Leads to Vitamin C Deficiency, Causing Cell Mitochondria DNA Mutation & Cancer

# 5

During phase 5, depleted adrenaline (epinephrine) levels cause a depletion of ascorbic acid (vitamin c) in the adrenal glands. Ascorbic acid is the main ingredient used by dopamine to make noradrenaline (norepinephrine) which is then converted to adrenaline. During prolonged chronic stress more and more adrenaline is pumped out and then depleted, meaning more and more ascorbic acid is used up in the creation of adrenaline. During chronic stress the adrenal glands also release ascorbic acid into the body to diminish the stressful impact of adrenaline [and other stress hormones] on the heart and blood pressure systems. Ascorbic acid is essential for preventing cell DNA damage caused by "oxidative stress", converting oxygen waste products 'superoxide' and 'hydrogen peroxide' into oxygen and water within the cell mitochondria during Oxidative Phosphorylation. The loss of ascorbic acid thereby increases cell mitochondrial DNA damage and cell mutation.

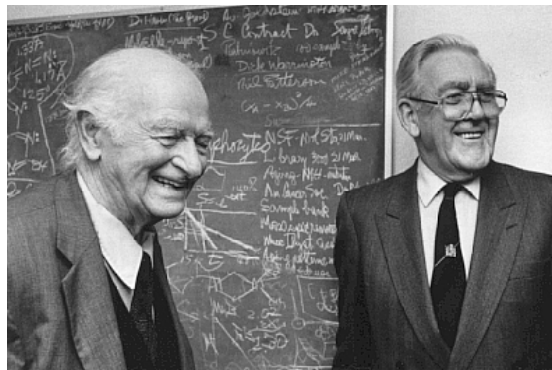


## The Theory

Ascorbic acid (vitamin c) is an essential nutrient required by the human body for survival. It is a key anti-oxidant used to breakdown superoxide and hydrogen peroxide in the mitochondria of cells, to prevent cell DNA damage and is an essential ingredient required by the adrenal glands to produce stress hormones, including norepinephrine and adrenaline. During prolonged chronic stress, ascorbic acid is used to create norepinephrine (noradrenaline) to be converted into epinephrine (adrenaline). Dopamine uses ascorbic acid and oxygen to synthesize norepinephrine via the pathway known as "dopamine β-hydroxylase" (also known as dopamine β-monooxygenase), and it is for this reason that 100 times more ascorbic acid is found in the adrenal glands than anywhere else in the body. During prolonged chronic stress, ascorbic acid is also released from the adrenal glands to protect the heart from cardiovascular disorders and arrhythmias. Yet as the condition of prolonged chronic stress continues for months and years and adrenaline levels are depleted, ascorbic acid (vitamin c) levels are also depleted as both are inextricably linked. Without an adequate supply of ascorbic acid [and other important anti-oxidants], superoxide and hydrogen peroxide are unable to be broken down into oxygen and water within the cell's mitochondria in the process known as Oxidative Phosphorylation, and normal cells are more likely to mutate into cancer cells due to cell DNA damage. Ewan Cameron [senior consulting physician at the Vale of Leven Hospital, Scotland] and Nobel Prize Laureate for his work in Chemistry, Linus Pauling PhD were convinced ascorbic acid should be included in the treatment of cancer and undertook a four year trial to determine the effectiveness of ascorbic acid (high dose vitamin c therapy) in 2,860 cancer patients between 1978-1982. The trial [below] involved a ten-day course of intravenous sodium ascorbic acid, followed indefinitely by 10-30 grams daily of oral ascorbic acid.

Ewan Cameron, MD: "As a single-handed surgeon working in a relatively small hospital, it would have taken me a decade or more to collect a sufficient number of identical patients with an identical type of cancer, all at the same stage of their

illness, to enable me to conduct a "proper" randomized double-blind clinical trial [of ascorbic acid]. We did the best we could; we conducted two controlled trials in which the survival time of groups of 100 cancer patients given supplemental ascorbate in the later stage of their illness was compared to the survival time of 1000 matched patients not given ascorbate. In the first study, the controls were selected "blind" by a young New Zealand doctor, specially employed for the purpose. I and a research assistant selected the controls for the second study. Both trials showed a definite survival advantage for the patients given ascorbate. These papers attracted world-wide media attention, and prompted a deluge of letters from cancer patients in many countries. Dr. Pauling and I wrote the book *Cancer and Vitamin C* in the hope of answering such questions, and lightening our mail-bags, but our effort has been unsuccessful. The letters and telephone calls continue unabated. Dan Rather of CBS network news in a recent broadcast stated that they estimated that 100,000 cancer patients in the United States were now taking vitamin C, with or without the tacit consent of their doctors. We have recently completed a four year trial involving 2,860 cancer patients attending three medium sized general hospitals in Scotland over the four year period from 1978 to 1982. This study was mainly funded by I.B.M. (United Kingdom) Ltd., who devised a computerized records system to suit our requirements. The data has been analyzed as follows: Firstly, patients who died within two weeks of first hospital attendance are excluded. Secondly, all patients who first attended the hospital less than six months before the study ended are also excluded. Finally, all patients who remain potentially cured (e.g. no known recurrence after primary curative surgery) are also excluded. This leaves 1,826 incurable cancer patients, some of whom received supplemental ascorbate (296) and the remainder (1532) who did not, effectively randomized by the date of first hospital attendance. The median survival time of the control patients, as measured from the date of first hospital attendance to the date of death (or to the end of the study, if still alive at that time), was 180 days, whereas the comparable time for the ascorbate group was 343 days. The results of this study, in much more detail, are contained in a manuscript submitted to The New England Journal of Medicine in 1984."



[Linus Pauling (left) and Ewan Cameron]

During normal cell respiration within the mitochondria, superoxide and hydrogen peroxide ( $H_2O_2$ ) are damaging by-products of Oxidative Phosphorylation that must be converted into oxygen and water to avoid cell damage. Ascorbic acid and the enzyme "superoxide dismutase" are the key substances used to convert these harmful substances into oxygen and water, thereby avoiding cell DNA damage and cell mutations. This is the anti-oxidant effect of ascorbic acid that occurs within normal cells to prevent cancer. Yet the body has ingeniously designed ascorbic acid to have the opposite effect inside cancer cells, where instead of it being used as an anti-oxidant to remove superoxide and hydrogen peroxide, it is used as a pro-oxidant to create superoxide and hydrogen peroxide to cause cell death within the cancer/tumor cell. In a landmark study conducted by the National Cancer Institute / National Institutes of Health, USA, researchers documented this pro-oxidant mechanism of ascorbic acid within tumor cell lines in mouse models and found high levels of intravenous ascorbic acid (vitamin c) significantly reduced tumor cell growth.

Mark Levine of the National Institutes of Health: "Ascorbic acid is an essential nutrient commonly regarded as an antioxidant. In this study, we showed that

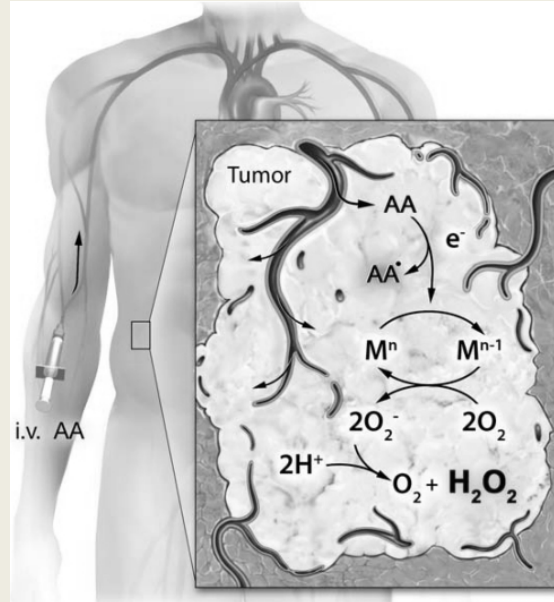
ascorbate at pharmacologic concentrations was a prooxidant, generating hydrogen-peroxide-dependent cyto-(cell) toxicity toward a variety of cancer cells *in vitro* without adversely affecting normal cells. To test this action *in vivo*, normal oral tight control was bypassed by parenteral ascorbate administration. Real-time microdialysis sampling in mice bearing glioblastoma [brain cancer] xenografts showed that a single pharmacologic dose of ascorbate (vitamin c) produced sustained ascorbate radical and hydrogen peroxide formation selectively within interstitial fluids of tumors but not in blood. Moreover, a regimen of daily pharmacologic ascorbate treatment significantly decreased growth rates of ovarian, pancreatic, and glioblastoma [brain] tumors established in mice. Similar pharmacologic concentrations were readily achieved in humans given ascorbate (vitamin c) intravenously. These data suggest that ascorbate as a prodrug may have benefits in cancers with poor prognosis and limited therapeutic options.

**Results:** Given their relative sensitivity, the efficacy of pharmacologic ascorbate administration on the growth of Ovar5, Pan02, and 9L tumors was examined in nude mice. Treatment commenced after tumors reached a palpable size of 5–7 mm in diameter. Xenograft experiments showed that parenteral ascorbate as the only treatment significantly decreased both tumor growth and weight by 41–53% for Ovar5 (ovarian), Pan02 (pancreas), and 9L (glioblastoma) tumors. Metastases, present in ≈30% of 9L glioblastoma controls, were absent in ascorbate-treated animals. These preclinical data provide a firm basis for advancing pharmacologic ascorbate in cancer treatment to humans. The tumor xenograft results are especially noteworthy because ascorbate (vitamin c), considered a nutrient, was used here only as a single-agent drug. Pharmacologic concentrations of ascorbate decreased tumor volumes 41–53% in diverse cancer types known for both their aggressive growth and limited treatment options.

**Discussion:** Ascorbate has a unique history in cancer treatment. Interest peaked over 30 years ago when retrospective data indicating possible benefit of high-dose ascorbate for patients with cancer were published. Subsequent double-blind placebo-controlled trials showing no benefit were considered definitive, and ascorbate treatment was dismissed by conventional oncologists. We revisited the controversy of ascorbate (vitamin c) in cancer therapy in light of several new observations. First, it was recognized that ascorbate was administered both intravenously and orally in the retrospective studies but only orally in the double-blind trials. Second, clinical and pharmacokinetics studies within the past 12 years indicate that oral [doses of] ascorbate produces concentrations in plasma and tissue that are tightly controlled (<0.2 mM). Our studies in rats demonstrated that pharmacologic concentrations of ascorbate in plasma (>0.2 mM) could be achieved only by circumventing oral tight control with parenteral (intravenous) administration. Third, complementary and alternative medicine practitioners continue to administer high-dose ascorbate off label, without apparent toxicity when patients are properly screened for normal renal function and absence of glucose-6-phosphate dehydrogenase deficiency, iron overload, and oxalate nephropathy. With such screening, data from a recent Phase I study show that i.v. ascorbate did not have adverse effects. These data coupled with the possibility of benefit suggested that further rigorous studies were warranted.

Our findings showed that pharmacologic ascorbic acid concentrations were cyto-(cell) toxic to many types of cancer cells *in vitro* and significantly impeded tumor progression *in vivo* without toxicity to normal tissues. The amelioration of ascorbate cytotoxicity *in vitro* by the addition of catalase was consistent among sensitive cancer cells and points unambiguously to H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide) generation in the extracellular medium. Hydrogen peroxide cytotoxicity is promiscuous in its action, compromising membranes, glucose metabolism, and DNA integrity. Variation in sensitivity among cancer cells may be related to the complex networks that H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide) acts on combined with the range of functional mutations intrinsic to each cancer cell line, which are not present in normal cells (EC<sub>50</sub> > 20 mM). Although the molecular basis for the

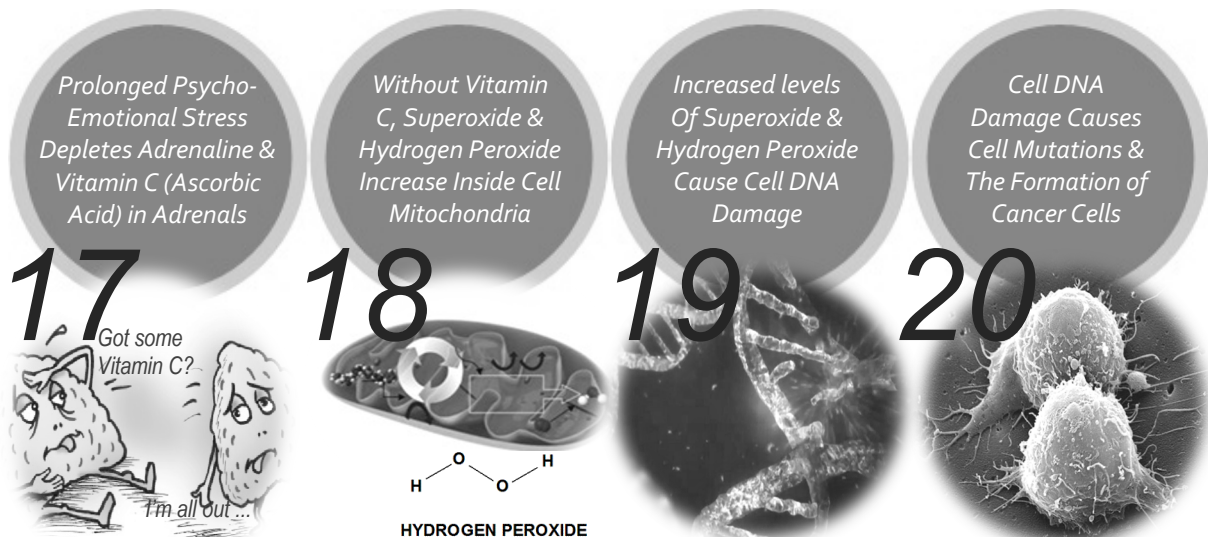
relative resistance of normal cells remains to be elucidated, the current *in vivo* data support that pharmacologic ascorbate (vitamin c) concentrations, which can readily be achieved in humans, diminished growth of several aggressive cancer types in mice without causing apparent adverse effects. Although our preclinical mouse data showed that tumor growth was significantly decreased, the use of pharmacologic ascorbate as a single agent was not curative. As modalities in cancer are often combined, these data suggest that pharmacologic ascorbate in combination with other therapies deserves further exploration for treatment of cancers that otherwise have poor outcomes, such as pancreatic and ovarian carcinomas and glioblastoma.”



Proposed mechanism for tumoricidal (tumor killing) actions of pharmacological ascorbate. Ascorbate (AA) distributes from the blood to the tumor extracellular fluid compartments after i.v. administration. In the tumor interstitium (within the tumor cell), ascorbate is oxidized to ascorbate radical (AA•) by a metalloprotein catalyst (M), which donates an electron ( $e^-$ ) to oxygen forming superoxide radical ( $O_2^-$ ) and ultimately the tumoricidal effector  $H_2O_2$  (hydrogen peroxide).

[<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2516281/>]

Within the 5<sup>th</sup> Phase of Cancer the following sequence of events can be observed in the cancer patient:



## The Evidence

The evidence for Phase 5 of Cancer can be broken down into the following components: a) the link between chronic stress and depleted ascorbic acid (vitamin c) levels within the body, b) the link between norepinephrine / adrenaline (epinephrine) synthesis/release and ascorbic acid (vitamin c) utilization/release via the dopamine  $\beta$ -hydroxylase (also known as dopamine  $\beta$ -monooxygenase) pathway, c) the link between ascorbic acid (vitamin c) depletion and cardiovascular (heart) protection during release of stress hormones, d) the link between ascorbic acid (vitamin c) depletion and increased levels of superoxide and hydrogen peroxide  $H_2O_2$  causing mitochondrial cell DNA damage, e) the link between mitochondrial cell DNA damage and cancer, f) the link between cancer and depleted levels of ascorbic acid (vitamin c) unable to synthesize hydrogen peroxide  $H_2O_2$  in cancer cells to induce cancer cell death.

### ➤ Evidence of the Link Between Chronic Stress and Depleted Ascorbic Acid (Vitamin C) Levels Within the Body

195. In a study conducted by the Department of Biochemistry, Istanbul Faculty of Medicine, University of Istanbul, researchers found rats exposed to chronic stress had decreased levels of ascorbic acid (vitamin c). "The effect of chronic stress (immobilization and cold) on hepatic and gastric thiobarbituric acid reactive substances (TBARS) and vitamin C levels were investigated in rats having long-term depletion of glutathione (GSH) by applying buthionine sulfoximine (BSO). GSH and vitamin C levels decreased and TBARS levels increased in the liver and stomach of rats subjected to [chronic] stress." [<http://www.ncbi.nlm.nih.gov/pubmed/9368915>]
196. In a study conducted by the Federal University of Santa Maria, researchers found rats exposed to chronic mild stress had decreased plasma levels of ascorbic acid (vitamin c). "This study investigated the influence of neonatal handling on behavioral and biochemical consequences of chronic mild stress (CMS) in adulthood. In adulthood, half the number of animals were exposed to CMS (chronic mild stress) for 3 weeks and submitted to behavioral testing, including sucrose preference (SP), elevated plus maze (EPM), and defensive burying tasks (DBTs), followed by biochemical assessments. CMS (chronic mild stress) reduced SP, increased anxiety in EPM and DBT, and increased adrenal weight. In addition, CMS (chronic mild stress) decreased plasma vitamin C (VIT C) levels and increased protein carbonyl (PC) levels, catalase (CAT) activity in [brain] hippocampus and cortex, and superoxide dismutase (SOD) levels in cortex." [<http://www.ncbi.nlm.nih.gov/pubmed/22998434>]
197. In a landmark joint study conducted by the Santokba Durlabhji Memorial Hospital, the Department of Home Science, University of Rajasthan, the Gautam Hospital & Research Center and Institute of Behavioural Sciences & Alternative Medicine, and the Department of Biochemistry, SMS Medical College, Jaipur, Rajasthan, India, researchers found patients with generalized anxiety disorder (GAD) and depression have significantly lower blood serum levels of ascorbic acid (vitamin c). "Anxiety and depression form commonest stress-induced psychiatric disorders. This study was carried out to find out whether patients with generalized anxiety disorder (GAD) and depression have any difference in blood serum levels of vitamins A ( $\beta$ -carotene), C, and E in comparison to the normal healthy control group and whether supplementation of adequate doses of vitamins A ( $\beta$ -carotene), C, and E leads to improvement in anxiety and depression and reduction in scores of the patients. Eighty subjects in the age group of 20–60 years, who attended a psychiatric clinic of a private hospital and who met inclusion and exclusion criteria of the study and consented for psychological evaluation and blood screening to find out the serum levels of vitamins A, C, and E, were included in the study. It was observed that patients with GAD (generalized anxiety disorder) and depression had significantly lower levels of vitamins A, C, and E in comparison to healthy controls. After dietary supplementation of these vitamins for a period of 6 weeks, a significant reduction in anxiety and depression scores of patients was observed. A significant increase in the blood levels of antioxidants was observed in patients except that of vitamin E in the group of depressed patients." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3512361/>]
198. In a study conducted by the Department of Epidemiology and Public Health (MH, GDM), University College London, researchers found depressed patients had lower plasma ascorbic acid (vitamin c) levels. "A total of 1,007 participants (522 men, 485 women; mean age:  $76.4 \pm 7.3$  years) [were included in this study]. At baseline, 20.9% of participants demonstrated depression. Depressed participants were at a higher relative risk of all cause mortality during follow-up. Low-grade inflammation and low plasma vitamin C were also independently associated with depression and mortality but did not explain any of the association between depression and mortality." [<http://www.ncbi.nlm.nih.gov/pubmed/20808095>]
199. In a study conducted by the Department of Psychology, University of Canterbury, Christchurch, New Zealand, researchers found rats pre-treated with ascorbic acid (vitamin c) had reduced anxiety under stress conditions. "Adult male and female hooded rats (about 110 days old) consumed vitamins C and E separately and

combined together in their drinking water and were assessed for anxiety approximately 50 and then 80 days later in an open field and an acoustic startle apparatus. They were tested when 160+ days old, and then again at 190+ days. For both testing ages combined, the vitamins and their combination increased open-field ambulation (movement) and occupancy of the four center squares of the apparatus. Treatment with vitamins C and E separately and combined together also decreased acoustic startle amplitude. It was suggested that decreases in anxiety produced by the vitamins may have arisen from their antioxidant properties, attenuation of [stress hormone] cortisol activity or some as yet undetermined effects on anxiety-related brain structures and neurotransmitters." [<http://www.ncbi.nlm.nih.gov/pubmed/21036190>]

200. In a study conducted by the Department of Biochemistry, Centre of Biological Science, Federal University of Santa Catarina, Brazil, researchers found mice exposed to chronic unpredictable stress caused depression and that subsequent administration of ascorbic acid (vitamin c) reversed the depressive-like symptoms. "Taking into account that experimental chronic unpredictable stress (CUS) induces depressive-like behavior and that ascorbic acid has antidepressant-like effect in animals, the objective of this study was to investigate the influence of ascorbic acid on depressive-like behavior induced by [the] CUS [chronic stress] paradigm, serum corticosterone levels and markers of oxidative stress in cerebral cortex and hippocampus of mice. Animals were submitted to [the] CUS (chronic unpredictable stress) procedure during 14 days. From the 8th to the 14th day mice received ascorbic acid (10 mg/kg) or fluoxetine (10 mg/kg, conventional antidepressant, positive control) once a day by oral route. On 15th day behavioral and biochemical parameters were analyzed. CUS (chronic un-predictable stress) exposure caused a depressive-like behavior evidenced by the increased immobility time in the tail suspension test and decreased time in which mice spent grooming in the splash test. Repeated ascorbic acid or fluoxetine administration significantly reversed CUS (chronic unpredictable stress)-induced depressive-like behavior and oxidative [cell] damage. These findings indicate a rapid and robust effect of ascorbic acid in reversing behavioral and biochemical alterations induced by CUS (chronic unpredictable stress) in mice, suggesting that this vitamin may be an alternative approach for the management of depressive symptoms." [<http://www.ncbi.nlm.nih.gov/pubmed/22154133>]

➤ Evidence of the Link Between Norepinephrine / Adrenaline (Epinephrine) Synthesis/Release and Ascorbic Acid (Vitamin C) Utilization/Release via the Dopamine  $\beta$ -Hydroxylase (Dopamine  $\beta$ -Monooxygenase) Pathway

201. In a study conducted by the Laboratory of Cell Biology and Genetics, National Institute of Diabetes, Digestive and Kidney Diseases, Maryland, researchers found ascorbic acid (vitamin c) and the magnesium-based ATP energy molecule are key components in converting dopamine to norepinephrine, a precursor to epinephrine (adrenaline). "Ascorbic acid and Mg-ATP were found to regulate norepinephrine biosynthesis in intact secretory vesicles synergistically and specifically, using the model system of isolated bovine chromaffin granules. Under these conditions of dopamine uptake, norepinephrine biosynthesis was enhanced 5-6-fold by Mg (magnesium)-ATP and ascorbic acid (vitamin c) compared to control experiments with dopamine only. Furthermore, norepinephrine formation was enhanced approximately 3-fold by ascorbic acid and Mg-ATP together compared to norepinephrine formation in granules incubated with either substance alone. Other physiologic reducing agents were not able to increase norepinephrine biosynthesis in the presence or absence of Mg (magnesium)-ATP. The mechanism of the effect of ascorbic acid and Mg (magnesium)-ATP on norepinephrine biosynthesis was investigated and appeared to be independent of a positive membrane potential. The effect was also not mediated by direct action of ADP, ATP, or magnesium on the activity of soluble or particulate dopamine beta-monooxygenase. These data indicate that Mg (magnesium)-ATP and ascorbic acid specifically and synergistically co-regulate dopamine beta-monooxygenase activity in intact chromaffin granules, independent of substrate uptake." [<http://www.ncbi.nlm.nih.gov/pubmed/3143726>]

202. In a further study conducted by the Laboratory of Cell Biology and Genetics, National Institute of Diabetes, Digestive and Kidney Diseases, Maryland, researchers found that dopamine  $\beta$ -monooxygenase is specifically stimulated by ascorbic acid (vitamin c) alone in the synthesis of norepinephrine, a precursor to adrenaline. "In resting cells, ascorbic acid increased dopamine beta-monooxygenase activity without changing tyrosine 3-monooxygenase activity. Norepinephrine specific activity was increased by ascorbic acid, while dopamine specific activity was unchanged. Enhancement of dopamine beta-monooxygenase activity was specific for ascorbic acid, since other reducing agents with higher redox potentials were unable to increase norepinephrine formation. The specific effect of ascorbic acid on enhancement of norepinephrine formation was also observed in chromaffin cells stimulated to secrete with carbachol, acetylcholine, veratridine, and potassium chloride. These data indicate that, under a wide variety of conditions, only one [norepinephrine] catecholamine biosynthetic enzyme activity, dopamine beta-monooxygenase, is specifically stimulated by ascorbic acid alone in cultured chromaffin (adrenal) cells." [<http://www.ncbi.nlm.nih.gov/pubmed/3711090>]

203. In a study conducted by the Department of Medicine, Vanderbilt University School of Medicine, Nashville, researchers found when dopamine was added to cells in culture, the ascorbic acid (vitamin c) present within the cells immediately converted the dopamine into norepinephrine [the precursor to adrenaline] via the dopamine  $\beta$ -hydroxylase pathway. "Ascorbic acid enhances synthesis of norepinephrine from dopamine in adrenal chromaffin cells by serving as a co-factor for chromaffin granule [to release norepinephrine hormone via] dopamine  $\beta$ -hydroxylase (D $\beta$ H). In this study we evaluated the stimulation of norepinephrine synthesis from dopamine in cultured SH-SY5Y neuroblastoma tumor cells. These cells contained neither ascorbate nor norepinephrine in culture, but when provided with dopamine, they generated intracellular norepinephrine at rates that were stimulated several-fold by intracellular ascorbate (vitamin c). Ascorbate-induced increases in norepinephrine synthesis in dopamine-treated cells were linear over 60 min, despite saturation of intracellular ascorbate. These results show that ascorbate promptly enhances norepinephrine synthesis from dopamine by neuronal cells; that it does so at physiologic intracellular concentrations in accord with the kinetics of [the] D $\beta$ H (dopamine  $\beta$ -hydroxylase pathway), and that it both protects cells from superoxide and by providing electrons to D $\beta$ H (dopamine  $\beta$ -hydroxylase)." [<http://www.ncbi.nlm.nih.gov/pubmed/23022576>]
204. In a study conducted by the Department of Hematology and Oncology, Children's Hospital, University of Tübingen, Germany, researchers found ascorbic acid (vitamin c) is essential for synthesis of norepinephrine from dopamine, but also essential for synthesis of dopamine and L-DOPA. "Ascorbic acid is well known to induce noradrenaline (norepinephrine) synthesis in sympathetic nervous cells. In a series of experiments we found that incubation of the neuroblastoma cell line SK-N-SH with ascorbic acid (100-500 microM) for 2 h results in a significantly enhanced synthesis of 3,4-dihydroxyphenylalanine (DOPA) and dopamine. In summary the data give evidence that ascorbic acid leads to enhanced DOPA production in SK-N-SH cells by two different mechanisms: at the metabolic level after short-term incubation and by increasing the tyrosine hydroxylase gene expression after long-term incubation." [<http://www.ncbi.nlm.nih.gov/pubmed/9578138>]
205. In a study conducted by the Department of Endocrinology, Heinrich-Heine-University, Düsseldorf, Germany, researchers found mice deficient in ascorbic acid (vitamin c) have significantly reduced norepinephrine and epinephrine (adrenaline) levels. "Ascorbic acid (vitamin C) is a cofactor required in catecholamine synthesis for conversion of dopamine to norepinephrine by dopamine beta-hydroxylase. Mutant mice lacking the plasma membrane ascorbic acid transporter (SVCT2) have severely reduced tissue levels of ascorbic acid and die after birth. We therefore investigated whether these mice might have impaired synthesis of [epinephrine / norepinephrine] catecholamines. Levels of catecholamines in brain were unaffected by SVCT2 deficiency. In heart, the only evidence for impaired dopamine beta-hydroxylase activity was a twofold increase in tissue dopamine. An influence of the deficiency on tissue catecholamines was most prominent in the adrenals where norepinephrine was decreased by 50% and epinephrine, by 81%. The data, however, establish a crucial role for ascorbic acid in adrenal chromaffin cell function." [<http://www.ncbi.nlm.nih.gov/pubmed/12897061>]
206. In a study conducted by the Molecular Regulation of Aging, Tokyo Metropolitan Institute of Gerontology, researchers found ascorbic acid (vitamin c) deficient mice had significantly decreased levels of adrenaline and noradrenaline. "In the adrenals of AA (-) (ascorbic acid deficient) SMP30/GNL KO mice, noradrenaline and adrenaline levels decreased significantly compared to other three groups of mice, although there were no significant differences in dopamine  $\beta$ -hydroxylase or phenylethanolamine N-methyltransferase mRNA content." [<http://www.ncbi.nlm.nih.gov/pubmed/23508458>]
- Evidence of the Link Between Ascorbic Acid (Vitamin C) Depletion and Cardiovascular (Heart) Protection During Release of Stress Hormones (Cortisol, Norepinephrine, Adrenaline)
207. In a landmark study conducted by the Department of Pharmacology, University of Edinburgh and Division of Biochemistry and General Nutrition of the Commonwealth Scientific and Industrial Research Organization, University of Adelaide, South Australia, researchers found adrenaline released into the bloodstream of rats resulted in a large depletion of ascorbic acid (vitamin c) in the adrenal glands. "The concentration of ascorbic acid in the adrenal gland of the rat was determined after the subcutaneous injection of l-adrenaline, l-noradrenaline, and dlisopropyl-noradrenaline (isoprenaline). A series of animals which received no injection but were otherwise kept under the same environmental conditions as the injected groups had an average concentration of ascorbic acid in the adrenal gland of 420 mg. /100 g. A large depletion was observed two hours after the injection of adrenaline and a much smaller depletion after that of noradrenaline. Isoprenaline is as potent as l-adrenaline in depleting ascorbic acid in the adrenal gland, in spite of the fact that it consists of 2 isomers." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1509216/pdf/bripharmchem00118-0127.pdf>]

208. In a study conducted by the Zoology Department, Faculty of Science, Suez Canal University, Ismailia, Egypt, researchers found stressed rats pretreated with wild honey [high in vitamin c] protected the heart against cardiac disorders during the administration of adrenaline (epinephrine). "Induction of hyperadrenergic activity (heightened anxiety) was experimentally achieved in urethane-anesthetized rats using epinephrine (adrenaline). Acute administration of epinephrine (100 microg/kg) for 2 hours induced several cardiac disorders and vasomotor dysfunction. Pretreatment with natural wild honey (5 g/kg) for 1 hour prior to the injection with epinephrine (100 mug/kg) protected the anesthetized normal rats from the incidence of epinephrine-induced cardiac disorders and vasomotor dysfunction. Moreover, posttreatment with natural wild honey (5 g/kg) following the injection with epinephrine (100 microg/kg) for 1 hour showed several ameliorative outcomes to the electrocardiographic parameters and vasomotor dysfunction of anesthetized stressed rats. Furthermore, natural wild honey preserved the positive inotropic (heart contraction) effect of epinephrine in both cases. Also, the total antioxidant capacity (AOC) of natural wild honey was found to be very pronounced. Levels of both reduced glutathione and ascorbic acid (vitamin C) were considered relatively high in natural wild honey." [<http://www.ncbi.nlm.nih.gov/pubmed/18361743>]
209. In a study conducted by the Department of Physiology, Faculty of Medicine, University of Natal, South Africa, researchers found the release of ascorbic acid (vitamin c) during chronic stress conditions plays an important role in modulating stress hormone levels to protect the heart. "The effects of vitamin C supplementation on the alterations in the circulating concentrations of cortisol, adrenaline, which accompany ultramarathon running were measured. Forty-five participants in the 1999 Comrades 90 km marathon were divided into equal groups (n = 15) receiving 500 mg/day Vit C (VC-500), 1500 mg/day Vit C (VC-1500) or placebo (P). Immediate post-race serum (stress hormone) cortisol was significantly lower in the VC-1500 group than in P (placebo) and VC-500 groups. When the data from VC-500 and P groups was combined (n = 17), immediate post-race plasma adrenaline were also significantly lower in the VC -1500 (high vitamin c) group. The study demonstrates an attenuation, albeit transient, of both the adrenal stress hormone and anti-inflammatory polypeptide response to prolonged exercise in runners who supplemented with 1500 mg vitamin C per day when compared to < or = 500 mg per day." [<http://www.ncbi.nlm.nih.gov/pubmed/11590482>]
210. In a study conducted by the Irma Lerma Rangel College of Pharmacy, Dept of Pharmaceutical Sciences, Texas A&M Health Science Center, researchers found ascorbic acid (vitamin c) protected rats from heart disorder arrhythmias during increased levels of adrenaline (epinephrine). "Since excessive amounts of [epinephrine] catecholamines are known to produce [heart] arrhythmias and increase the plasma level of aminochrome, an oxidation product of catecholamines, we tested the hypothesis that antioxidants may reduce the formation of aminochrome and prevent the catecholamine-induced arrhythmias. For this purpose, Sprague-Dawley rats were pretreated orally, with vitamin A or vitamin C for 21 days, and their effects on ventricular arrhythmias induced by a bolus dose or cumulative doses of intravenous epinephrine were examined. Electrocardiogram recording of these animals revealed that pretreatment with either of these vitamins increased the time of onset and decreased the duration of the epinephrine-induced ventricular [heart] arrhythmias. Ventricular fibrillations due to high doses of epinephrine were also prevented by the antioxidant pretreatment." [<http://www.ncbi.nlm.nih.gov/pubmed/19763903>]
211. In a meta-analysis of 29 studies conducted by the Johns Hopkins School of Medicine, Maryland, researchers found ascorbic acid (vitamin c) is used by the body to reduce blood pressure caused by stress on the heart. "The objective was to conduct a systematic review and meta-analysis of clinical trials that examined the effects of vitamin C supplementation on BP (blood pressure). Twenty-nine trials met eligibility criteria for the primary analysis. The median dose was 500 mg/d, the median duration was 8 wk, and trial sizes ranged from 10 to 120 participants. In short-term trials, vitamin C supplementation reduced SBP (systolic blood pressure) and DBP (diastolic blood pressure)." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325833/>]
- Evidence of the Link Between Ascorbic Acid (Vitamin C) Depletion and Increased Levels of Superoxide and Hydrogen Peroxide H<sub>2</sub>O<sub>2</sub> (Known as Reactive Oxygen Species or ROS) Causing Mitochondrial Cell DNA Damage
212. In a study conducted by the Cancer and Ageing Research Group, School of Biomedical Sciences, University of Ulster, Northern Ireland, researchers found smokers consuming ascorbic acid (vitamin c) had significantly decreased levels of hydrogen peroxide H<sub>2</sub>O<sub>2</sub>-induced cell DNA damage. "In this study, the potential protective effect of vitamin C or E supplementation in vivo against endogenous (naturally occurring) and H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide)-induced DNA damage levels in [peripheral blood cell] lymphocytes was assessed. The supplementation involved fourteen healthy male and female non-smokers mean age 25-53 (SD 1.82) years, who were asked to supplement an otherwise unchanged diet with 1000 mg vitamin C daily for 42 d or 800 mg vitamin E daily for 42 d. Supplementation with vitamin C or vitamin E decreased significantly H<sub>2</sub>O<sub>2</sub>



(hydrogen peroxide)-induced DNA damage in PBL (peripheral blood cell lymphocytes), but had no effect on endogenous (normal) levels of DNA damage." [<http://www.ncbi.nlm.nih.gov/pubmed/11029970>]

213. In a study conducted by the Department of Cell Biology and Histology, Sackler Faculty of Medicine, Tel-Aviv University, researchers found cell mitochondria treated with ascorbic acid (vitamin c) prior to exposure to hydrogen peroxide  $H_2O_2$  had a reduction in the accumulation of peroxides. "We investigated peroxide and superoxide accumulation, cytochrome c nature and release from mitochondria, as well as caspase activation during exposure of HL-60 cells to  $H_2O_2$  (hydrogen peroxide) and the protective effect of ascorbic acid (vitamin c). Exposure of the cells to 100 microM  $H_2O_2$  (hydrogen peroxide) resulted in intracellular accumulation of peroxides, denaturation of cytochrome c that was identified in the [cell] mitochondria and cytosol, release of native cytochrome c to the [cell] cytosol and fall in mitochondrial membrane potential ( $\Delta\Psi(m)$ ). Loading of cells with ascorbic acid (vitamin c) before exposure to  $H_2O_2$  (hydrogen peroxide) resulted in a dose-dependent protective effect against: intracellular accumulation of peroxides,  $\Delta\Psi(m)$  alteration, cytochrome c denaturation and release." [<http://www.ncbi.nlm.nih.gov/pubmed/11960609>]
214. In a study conducted by the Department of Pathology, College of Veterinary Medicine, Kyungpook National University, Republic of Korea, researchers found ascorbic acid (vitamin c) deficient mice had increased ROS (reactive oxygen species); the governing term used to describe increased superoxide and hydrogen peroxide  $H_2O_2$  levels. "Significantly decreased levels of reactive oxygen species, MDA (malondialdehyde) and HAE (4-hydroxyalkenals) were detected in KO + VC (vitamin c knock-out) mice compared with KO (vitamin deficient) mice. Therefore, it is concluded that vitamin C deficiency induces an increase of CYP2E1 expression and elevated ROS (reactive oxygen species ↔ superoxide and hydrogen peroxide) production, which causes oxidative liver injury and the elevation of hepatocyte binucleation (liver cell nucleus mutation) in SMP30 KO mice." [<http://www.ncbi.nlm.nih.gov/pubmed/21039840>]
215. In a study conducted by the Department of Pharmacology, Weill Medical College, Cornell University, New York, researchers found loading cell mitochondria with ascorbic acid (vitamin c) prevented ROS (reactive oxygen species ↔ superoxide and hydrogen peroxide  $H_2O_2$  levels) and also inhibited mitochondrial cell DNA damage. "Reactive oxygen species (ROS)-induced [cell] mitochondrial abnormalities may have important consequences in the pathogenesis of degenerative diseases and cancer. Vitamin C is an important anti-oxidant known to quench (extinguish) ROS (superoxide/ $H_2O_2$ -induced reactive oxygen species), but its mitochondrial transport and functions are poorly understood. We found that the oxidized form of vitamin C, dehydroascorbic acid (DHA), enters [cell] mitochondria via facilitative glucose transporter 1 and accumulates mitochondrially as ascorbic acid. Loading mitochondria with AA (ascorbic acid) quenched (extinguished) mitochondrial ROS and inhibited oxidative mitochondrial DNA damage. Our results show that analogous to the cellular uptake, vitamin C enters mitochondria in its oxidized form via Glut1 (glucose transporter 1) and protects [cell] mitochondria from oxidative injury." [<http://www.ncbi.nlm.nih.gov/pubmed/16195374>]
216. In a study conducted by the Department of Health Toxicology, School of Public Health, Central South University, China, researchers found ascorbic acid (vitamin c) protected the mitochondria of cells from cell DNA damage caused by the chemical toxin hexavalent chromium increasing ROS (reactive oxygen species ↔ superoxide and hydrogen peroxide  $H_2O_2$ ) levels. "In the present study by using peripheral blood lymphocytes (cells) from Sprague-Dawley rats, we demonstrated that vitamin C (ascorbic acid) pre- and co-treatment have a protective effect against Cr(VI) (hexavalent chromium)-induced loss of cell viability and mitochondrial [cell DNA] damage, while only vitamin C co-treatment has a protective effect against the Cr(VI)-induced increase in DPCs. The mechanistic investigation revealed that cellular reactive oxygen species levels are correlated with Cr(VI)-induced mitochondrial damage, and that p53 expression is correlated with the Cr(VI)-induced increase in DPCs (DNA protein crosslinks that prevent normal DNA replication). We concluded that vit C exerts different time-order effects on Cr(VI)-induced mitochondrial [cell] damage and DPC (DNA protein crosslink) formation, and that biomarkers, including DPC and p53, may be used in the assessment of the development of Cr(VI)-induced cancer." [<http://www.ncbi.nlm.nih.gov/pubmed/23657841>]
217. In a study conducted by the Tokyo Metropolitan Institute of Gerontology, researchers found vitamin c deficient mice had significantly higher superoxide levels, the precursor to hydrogen peroxide  $H_2O_2$ . "Vitamin C (VC) has a strong antioxidant function evident as its ability to scavenge superoxide radicals in vitro. We verified that this property actually exists in vivo by using a real-time imaging system for detecting superoxide in (SMP30)/(GNL) knockout (KO) mice, which cannot synthesize vitamin c in vivo. SMP30/GNL KO mice were given 1.5 g/L vitamin c for 2, 4, or 8 weeks or denied vitamin c. At 4 and 8 weeks, vitamin c levels in brains from vitamin deficient KO mice were [less than] 6% of that in vitamin c administered KO mice. Accordingly, superoxide-dependent chemi-luminescence levels were 3.0-fold and 2.1-fold higher, respectively, in vitamin

c deficient KO mice than in vitamin c administered KO mice. Thus, vitamin c depletion specifically increased superoxide generation in a model of the living brain." [<http://www.ncbi.nlm.nih.gov/pubmed/18848523>]

218. In a study conducted by the Department of Anesthesiology and Critical Care, University Clinical Hospital, Valencia, Spain, researchers found ascorbic acid (vitamin c) protected cells exposed to the toxic drug AZT from mitochondrial cell DNA damage caused by an increase in ROS (reactive oxygen species ↔ superoxide and hydrogen peroxide H<sub>2</sub>O<sub>2</sub>) levels. "Animals treated with antioxidant vitamins were fed the same diet as controls but supplemented with vitamins C (ascorbic acid, 10 g/ kg diet) and E (0.6 g/kg diet) for 65 days. Cardiac mitochondrial [cell] DNA (mtDNA) of mice treated with AZT had over 120% more oxo-dG [which is a biomarker of oxidative damage to DNA] in their mitochondrial DNA than untreated controls. AZT treatment also caused an increase in mitochondrial lipid peroxidation [caused by increased superoxide and hydrogen peroxide H<sub>2</sub>O<sub>2</sub> levels] and an oxidation of mitochondrial glutathione. Dietary supplementation with supra-nutritional doses of the antioxidant vitamins C and E protected against these signs of mitochondrial oxidative stress. The oxidative effects of AZT are probably due to an increase in production of reactive oxygen species by mitochondria of AZT-treated animals, raising the possibility that oxidative stress may play an important role in the cardiotoxicity of AZT." [<http://www.ncbi.nlm.nih.gov/pubmed/15501479>]
219. In a study conducted by the Department of Biochemistry, College of Medicine, Hallym University, Korea, researchers found ascorbic acid (vitamin c) reduced mitochondrial cell DNA damage and increased cell life-span by dramatically decreasing the formation of ROS (reactive oxygen species ↔ superoxide and hydrogen peroxide H<sub>2</sub>O<sub>2</sub>). "Continuous treatment of HEF cells with ascorbic acid (at 200 μM) increased maximum PD (population cell doubling) numbers by 18% and lowered SA-β-gal positive staining, an aging marker, by 2.3 folds, indicating that ascorbic acid extends replicative life span of HEF cells. Ascorbic acid treatment lowered DCFH [a measure of reactive oxygen species ↔ superoxide and hydrogen peroxide H<sub>2</sub>O<sub>2</sub>] by about 7 folds and Rho123 by about 70%, suggesting that ascorbic acid dramatically decreased ROS (reactive oxygen species ↔ superoxide and hydrogen peroxide H<sub>2</sub>O<sub>2</sub>) formation. Ascorbic acid also increased aconitase activity, a marker of mitochondrial [cell] aging, by 41%, indicating that ascorbic acid treatment restores age-related decline of mitochondrial [cell] function. Analysis of AP (apurinic/aprimidinic) [DNA damaged] sites showed that ascorbic acid treatment decreased AP [DNA damaged] site formation by 35%. Taken together, the results suggest that ascorbic acid extends replicative life span of HEF cells by reducing mitochondrial and DNA damages through lowering cellular ROS." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882584/>]

➤ Evidence of the Link Between Mitochondrial Cell DNA Damage (Mutation) and Cancer

220. In a groundbreaking study conducted by the Genesis Genomics Inc., Canada, researchers found all cases of malignant cancer harboured mitochondrial cell DNA mutations compared to benign tissue samples. "Here we report somatic mitochondrial DNA mutations from three specific tissue types (tumor, adjacent benign, and distant benign) recovered from 24 prostatectomy samples. Needle biopsy tissue from 12 individuals referred for prostate biopsy, yet histologically benign, were used as among individual control samples. We also sampled blood from each patient to serve as within individual controls relative to the somatic tissues sampled (malignant, adjacent, and distant benign). Complete mitochondrial [cell] genome sequencing was attempted on each sample. In contrast to both control groups [within patient (blood) and among patient (symptomatic benign)], all of the tissue types recovered from the malignant group harbored significantly different mitochondrial [cell] DNA (mtDNA) mutations." [<http://www.ncbi.nlm.nih.gov/pubmed/16825503>]
221. In a study conducted by the Dept of Pharmacology, School of Medicine, National Yang-Ming University, Taiwan, researchers found a high degree of mitochondrial cell DNA mutation in the DNA replicating D-Loop of those with various types of cancer. "In this study, we analyzed the nucleotide sequence of the D-loop and the copy number of mtDNA (mitochondrial DNA) in 54 hepatocellular carcinomas (HCCs), 31 gastric, 31 lung, and 25 colorectal cancers as well as their corresponding non-tumorous tissues. The results revealed that 42.6% (23/54) of the HCCs (hepatocellular carcinomas), 51.6% (16/31) of the gastric cancers, 22.6% (7/31) of the lung cancers, and 40.0% (10/25) of the colorectal cancers harbored mutation(s) in the D-loop of mtDNA. It is noteworthy that the incidence of somatic mutations in the D-loop of mtDNA (mitochondrial DNA) in the cancers of later stages was higher than that of the early-stage cancers. Taken together, our findings suggest that instability in the D-loop region of mtDNA, together with the decrease in mtDNA copy number, is involved in the carcinogenesis of human cancers." [<http://www.ncbi.nlm.nih.gov/pubmed/15965052>]
222. In a study conducted by the Institute for Molecular and Human Genetics, Georgetown University Medical Center, Washington, researchers found a high level of mitochondrial cell DNA mutation in tumors. "Somatic mitochondrial DNA alteration is a general phenomenon that occurs in cancerous cells. Although numerous

mtDNA (mitochondrial DNA) mutations have been identified in various tumors, the pathogenic significance of these mutations remains unclear. In order to better understand the role of mtDNA (mitochondrial DNA) mutations in the neoplastic process of oral cancer, the occurrence of mtDNA mutations in oral squamous cell carcinomas was screened by temporal temperature gradient gel electrophoresis (TTGE). Fourteen of 18 (77.8%) tumors had somatic mtDNA mutations with a total of 26 mutations. Among them, 6 were in mRNA coding region. Three were missense mutations (C14F, H186R, T173P) in NADH dehydrogenase subunit 2 (ND2). One frameshift mutation, 9485delC, was in cytochrome c oxidase subunit III. Eight (44%) tumors had insertion or deletion mutations in the np303-309 poly C region of the D-loop. Our results demonstrate that somatic mtDNA mutations occur in oral cancer." [http://www.ncbi.nlm.nih.gov/pubmed/15126307]

223. In a study conducted by the Department of Otolaryngology-Head and Neck Surgery, Head and Neck Cancer Research Division, Johns Hopkins University School of Medicine, researchers found mutations (alterations) in mitochondrial DNA to be commonplace in cancer development. "Mitochondrial DNA (mtDNA) alterations are associated with various cancer types, suggesting that the mitochondrial [cell] genome may be a critical contributing factor in carcinogenesis. We examined mtDNA content in 25 pairs of normal and tumor breast tissue samples, 37 papillary thyroid carcinoma (PTC), 21 benign thyroid neoplasms and in 20 paired normal and PTC samples. Our results showed that mtDNA (mitochondrial DNA) content was reduced in 80% of the breast tumors relative to their corresponding normal. mtDNA was increased in papillary thyroid carcinomas, however, when compared to the corresponding normal DNA taken from the same individual. Also, mtDNA content was increased in none-paired PTC samples compared to the normal controls. Our findings indicate that changes in mtDNA (mitochondrial DNA) content during carcinogenesis may be regulated in a tumor specific manner." [http://www.ncbi.nlm.nih.gov/pubmed/15856456]

➤ Evidence of the Link Between Cancer and Depleted Levels of Ascorbic Acid (Vitamin C) Unable To Synthesize Hydrogen Peroxide  $H_2O_2$  in Cancer Cells to Induce Cancer Cell Death

224. In a study conducted by the Molecular and Clinical Nutrition Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, researchers found ascorbic acid (vitamin c) to be a powerful tool for generating Hydrogen Peroxide  $H_2O_2$  to initiate cancer cell death. "Our goals here were to test whether ascorbate (vitamin c) killed cancer cells selectively, and if so, to determine mechanisms, using clinically relevant conditions. For five of the nine cancer cell lines, ascorbate (vitamin c) concentrations causing a 50% decrease in [cancer] cell survival were less than 5 mM, a concentration easily achievable from i.v. (intravenous) infusion. All tested normal cells were insensitive to [a higher amount of] 20 mM ascorbate. [In addition] four cancer cell lines were incubated with 5 mM ascorbate (vitamin c) or untreated media for 1 hour. Cells were diluted and plated and growth assessed after 14 days. All four untreated cell lines grew in soft agar, whereas three of four [cancer cell lines] exposed to ascorbate displayed at least 99% growth inhibition. Human lymphoma cells (JLP-119) were studied in detail to determine the effects of ascorbate on cell death. Ascorbate [thereby] induced concentration-dependent cell death, which was nearly 100% at 2 mM. Cell death was independent of metal chelators and absolutely dependent on  $H_2O_2$  (hydrogen peroxide) formation. Taken together, these data indicate that ascorbate (vitamin c) at concentrations achieved only by i.v. administration may be a pro-drug for formation of  $H_2O_2$  (hydrogen peroxide), and that blood can be a delivery system of the pro-drug to tissues." [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1224653/]

225. In a study conducted by the Division of Urologic and Transplantation Surgery, University of Massachusetts Medical Center, researchers found ascorbic acid (vitamin c) generating hydrogen peroxide  $H_2O_2$  is a potent treatment for killing prostate cancer cells. "Androgen-independent (DU145) and androgen-dependent (LNCaP) human prostate cancer cell lines were both treated in vitro with vitamin C (0-10 mM). Treatment of DU145 and LNCaP (prostate cancer) cells with vitamin C resulted in a dose- and time-dependent decrease in cell viability and thymidine incorporation into DNA. Vitamin C induced these changes through the production of hydrogen peroxide ( $H_2O_2$ ); addition of catalase (100-300 units/ml), an enzyme that degrades hydrogen peroxide, inhibited the effects of ascorbic acid. Our results suggest that ascorbic acid is a potent anticancer agent for prostate cancer cells." [http://www.ncbi.nlm.nih.gov/pubmed/9254898]

226. In a study conducted by the Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, researchers found hydrogen peroxide  $H_2O_2$  generated by ascorbic acid (vitamin c) successfully kills leukemia cells. "L-Ascorbic acid (LAA) is being investigated clinically for the treatment of patients with acute myeloid leukemia (AML) based on the observed effects of LAA (ascorbic acid) on AML (acute myeloid leukemia) progenitor cells in vitro. LAA (ascorbic acid) at concentrations of 0.25-1.0 mM induced a dose- and time-dependent inhibition of proliferation in three AML (acute myeloid leukemia) cell lines and also in leukemic cells from peripheral blood specimens obtained from three patients with AML. Flow cytometric analysis

showed that LAA (ascorbic acid) at concentrations of 0.25-1.0 mM could significantly induce apoptosis (cell death) in the AML (acute myeloid leukemia) cell lines. LAA (ascorbic acid) induced oxidation of glutathione to oxidized form and subsequent H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide) accumulation in a concentration-dependent manner, in parallel to induction of apoptosis (cell death). The direct role of H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide) in the induction of apoptosis (cell death) in AML (acute myeloid leukemia) cells was clearly demonstrated by the finding that catalase could completely abrogate (block) LAA-(ascorbic acid)-induced apoptosis (cell death). In conclusion, LAA (ascorbic acid) can induce apoptosis (cell death) in AML (acute myeloid leukemia) cells, and this is clearly due to H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide) which accumulates intracellularly as a result of oxidation of reduced glutathione by LAA (ascorbic acid)." [<http://www.ncbi.nlm.nih.gov/pubmed/15313465>]

227. In a landmark study conducted by the Dept of Surgery, University of Iowa College of Medicine, researchers found hydrogen peroxide H<sub>2</sub>O<sub>2</sub> generated by ascorbic acid (vitamin c) successfully inhibits the growth of nearly all pancreatic cancer cell lines, in vitro and in vivo. "We hypothesized that ascorbate concentrations achievable with i.v. dosing would be cytotoxic in pancreatic cancer for which the 5-year survival is <3%. Pancreatic cancer cell lines were treated with ascorbate (0, 5, or 10 mmol/L) for 1 hour, then viability and clonogenic survival were determined. Pancreatic tumor cells were delivered s.c. into the flank region of nude mice and allowed to grow at which time they were randomized to receive either ascorbate (4 g/kg) or osmotically equivalent saline (1 mol/L) i.p. for 2 weeks. There was a time- and dose-dependent increase in measured H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide) production with increased concentrations of ascorbate. Ascorbate decreased viability in all pancreatic cancer cell lines but had no effect on an immortalized pancreatic ductal epithelial cell line. Ascorbate decreased clonogenic survival of the pancreatic cancer cell lines, which was reversed by treatment of cells with scavengers of H<sub>2</sub>O<sub>2</sub>. Treatment with ascorbate (vitamin c) induced a caspase-independent cell death that was associated with autophagy. In vivo, treatment with ascorbate inhibited tumor growth and prolonged survival." [<http://www.ncbi.nlm.nih.gov/pubmed/20068072>]
228. In a study conducted by the Program in Integrative Medicine, University of Kansas Medical Center, Missouri, researchers found hydrogen peroxide H<sub>2</sub>O<sub>2</sub> generated by ascorbic acid (vitamin c) induced cell death in all tested cancer cell lines and significantly reduced pancreatic tumor volume in mice. "The results showed that pharmacologic AA (ascorbic acid) induced cytotoxicity (cell death) in all tested cancer cells, with IC(50) less than 4 mM, a concentration easily achievable in humans. Treatment in mouse pancreatic cancer xenografts showed that intraperitoneal AA (ascorbic acid) at 4 g/kg daily reduced tumor volume by 42%. Although all treatments (AA, GSH [glutathione], and AA+GSH) improved survival rate, AA+GSH inhibited the cytotoxic effect of AA alone and failed to provide further survival benefit. These data confirm the pro-oxidative anti-cancer mechanism of pharmacologic AA (ascorbic acid) and suggest that AA and GSH administered together provide no additional benefit compared with AA alone." [<http://www.ncbi.nlm.nih.gov/pubmed/21672627>]
229. In a groundbreaking study conducted by the Fukuoka Torikai Hospital and Kamioka Kozan Hospital, Japan, researchers found terminal cancer patients administered large oral doses of ascorbic acid (vitamin c) had significantly longer survival rates than those on low doses. "Clinical trials administering supplemental ascorbate (vitamin c) to terminal cancer patients were conducted at two hospitals in Japan. During the period 1973-1977 there were 99 patients with terminal cancer at the Fukuoka Torikai Hospital. The average times of survival after the date of designation as terminal were 43 days for 44 low-ascorbate patients and 246 days for 55 high-ascorbate patients. Three of the high-ascorbate patients were still alive, their average survival being 1550 days, on April 1, 1980. Similar effectiveness of ascorbate (vitamin c) was also observed at the Kamioka Kozan Hospital. There were 31 patients with terminal cancer during the period 1975-1979. The average survival times were 48 days for 19 control patients and 115 days for 6 high-ascorbate patients. One of the high-ascorbate patients was still alive, his survival being 215 days. In addition to the increase in survival times, the administration of large doses of ascorbate (vitamin c) seemed to improve the quality of life." [<http://www.ncbi.nlm.nih.gov/pubmed/6811475>]
230. In a joint study conducted by Nobel Prize Laureate Linus Pauling and Ewan Cameron of the Vale of Leven Hospital, Scotland, terminal cancer patients increased survival dramatically with high dose oral ascorbic acid (vitamin c). "A study has been made of the survival times of 100 terminal cancer patients who were given supplemental ascorbate, usually 10 g/day, as part of their routine management and 1000 matched controls, similar patients who had received the same treatment except for the ascorbate (vitamin c). The ascorbate-treated patients were found to have a mean survival time about 300 days greater than that of the controls. Survival times greater than 1 yr after the date of untreatability were observed for 22% of the ascorbate-treated patients and for 0.4% of the controls. The mean survival time of these 22 ascorbate-treated patients is 2.4 yr after reaching the apparently terminal stage; 8 of the ascorbate-treated patients are still alive, with a mean survival time after untreatability of 3.5 yr." [<http://www.ncbi.nlm.nih.gov/pubmed/279931>]

# The 6<sup>th</sup> Phase of Cancer



Prolonged Stress Results in a Subconscious Wanting to Die, Which Shuts Down the Immune System enabling Fungus & Cancer to Grow

Phase

6

During phase 6, the immune system is shut down by a subconscious wanting to die, caused by elevated stress hormone cortisol levels depleting serotonin and dopamine levels in the brain that cause internal depression. As revealed by God, an individual experiencing Inescapable Shock and prolonged chronic stress often feels tired of life and deep down wants out of the never-ending struggle and pain of life, sending subliminal messages to the immune system to shut down. This occurs at the subconscious level where the immune system receives orders to stop production of interleukin-2-producing T cells, B cells, natural killer cells, macrophages and neutrophils. Without immune system cells, viral-bacterial-yeast-like-fungus that have pleomorphised within cells continue to grow and newly created cancer cells continue to multiply.

## The Theory

In 1982, the Holy Spirit of God revealed in the following transcript that cancer manifests in the body as a result of the immune system being shut down caused by a subconscious wanting to die, known as the subconscious death wish. While at the conscious level the individual with cancer usually has a strong desire and will to live, it is at the deeper feeling level – the level of the subconscious mind – that the individual with cancer feels overwhelmed by the pain and struggle of life, sending subliminal thoughts to the immune system to shut down and exit life.

The Holy Spirit of God: "This Awareness indicates that, basically, the real cause of cancer is related unto the death wish. That the cancer conditions are prevalent in most entities (human beings), but the bodies of those who wish to continue living, who have enthusiasm for life, and who are loving and feel loved, these bodies generally are too healthy for cancerous conditions to gain control of their cells. This Awareness suggests that essentially the death wish is that which is the culprit. That this death wish can be very subtle, and often entities have mixed feelings and do not even realize they have had a death wish. This Awareness indicates that this can often be caused by a rejection of one who was loved. This can be caused by the loss of a loved one. This can be caused by an entity feeling unloved and unwanted, or rejected, and in this kind of attitude, the cancerous condition can begin to grow.

This Awareness indicates that even after the situation changes, and the entity finds new desire for life and new hope, the condition which began earlier may have gained a kind of foothold in the body and may continue having its effect. This Awareness indicates that in such a situation, the entity now wishing to live but having cancer, must go through a strong mental and emotional cleansing in order to throw off that cancerous condition which was invited in during that period wherein the death wish was felt. This Awareness indicates there have been many entities who have had cancer and have healed themselves, simply by the sheer will to be well. This Awareness indicates that the mind is the builder, and wherein one can accept a healing, half of the battle is won; the body tends to follow the directions of the mind. This Awareness suggests that wherein entities are convinced that there is no hope, then the situation follows that conviction. This Awareness indicates that essentially, the death wish is that which begins affecting the cells of the body to inform them as how to function, thus affecting the metabolism by creating certain attitudes within each cell as to what its function is. The attitudes within each cell, reflecting the attitude of the individual, can emanate a poisonous effect on those energies roundabout, or can

emanate a healthy effect, depending on the attitude. This Awareness indicates that wherein an entity (an individual) has a healthy attitude, a love for life, does not feel overstressed or overworked to the point of despair, or wishing to throw in the towel; this Awareness indicates that the cells feel likewise, and their orders from headquarters (the subconscious mind) are to repair themselves when given the opportunity, when given the proper nourishment, and to rest and restore themselves as much as is possible under the circumstances.

This Awareness indicates however, whenever the entity's attitude is such that "No one cares for me, I have no purpose in life, I might as well simply die", and the entity begins wishing to die, whether consciously or subconsciously, the cells then having received their message from headquarters, begin carrying out the orders: "Self-destruct! Self-destruct! Self-destruct! It is time for Self-destruct!" And whatever energies are brought in as sustenance, food or nourishment is simply poisoned or rejected on the orders from headquarters. This Awareness indicates that once the cells have the action in motion, then the entire system begins shutting down its life-force activities of whether the entity is eating this food or that, regardless of what is occurring; the cells are responding to the direct orders from headquarters.

This Awareness indicates if those orders have not changed by an equal or greater intensity from headquarters (subconscious mind), then the cells continue in their action. This Awareness indicates for example, if the headquarters sends forth an extremely volatile and highly-charged emotional message with an amplitude (force) of 144 or more, that states "This entity wishes to die", the cells then, carrying out this intense, highly amplified message, will not respond and reverse their action until an equal or greater message comes through. The headquarters then may send forth a message: "Oh, my God, I am dying from cancer and I don't really want to do this!" This Awareness indicates if this message is at an amplitude of 140 in comparison to the previous message of 144, the cancer will continue, although it will be greatly reduced in speed. This Awareness indicates that if, however, the entity's message in terms of emotional amplitude is: "Oh, my God, I am dying from cancer. I do not wish to do this. I have made a mistake. I want to live!" And if this amplitude is of a greater level than 144, - for example 150, the energies then may be such that the entity begins to improve, and if this amplitude can be continued, the improvement will continue. This Awareness indicates however, if the entity's amplitude is of 200, for example, the entity may have a miraculous cure, whereby the cancer begins to diminish rapidly.

This Awareness indicates that in understanding the power of the mind in healing the body, entities must also understand the nature of the amplitude or volume of emotions, and accompanying faith. For if one simply has an emotion of wanting to live, but accepts death through the message of fear, whereby the mind sends a message to the cells: "Oh, my God, I have cancer and the death-rate of this disease is almost certain" -- this Awareness indicates that even though this amplitude may have topped the original amplitude which caused the disease, all this message does is reinforce to the cells that they have started a process of shutting down, leading to death, and now they are to become aware of the danger of the action and that it is almost certain.

This Awareness indicates the cells then, recognizing that their action of shutting down and proceeding toward death is following directions, and new directions has been given which state that it is almost certain that mission will be completed. This Awareness indicates the fact that there is a fear accompanying the message does not inform the cells that they are to stop the action. This Awareness indicates however, wherein there is a message from headquarters (the subconscious mind) stating that the action which was started must be stopped at all cost, then no further movement in that direction shall be allowed, and any cell continuing this type of action will be reprimanded; this Awareness indicated then the cells have a clear and direct message. This Awareness

indicates as long as this message is consistent and of a higher amplitude than the original message, the cells recognize and receive their orders from headquarters and know that the orders have been changed and that reverse action must occur.

This Awareness indicates that wherein the cells receive the message that everything is going to be alright, repair is occurring, the cells are beginning to reverse their action and health is being restored to the system; this Awareness indicates this created an enthusiasm among the cells, who feel that "great! We don't have to self-destruct after all," and the cells begin working even more excitedly in the healing process. This Awareness indicates that the action of herbs, vitamins, minerals and nutrients upon the cell is much like giving medicine to children or to entities (persons), whereby the faith is enhanced along with the nutrient that is given. The medicine is given; it may be nothing more than water. But if the child is told, "This is magic water which will heal you," and if the child believed this to be so, then the child accepts the healing which is to follow and the cells are directed by the headquarters' thought to become healed.

This Awareness indicates that therefore, the proper medicine, while being more beneficial than mere water, or a placebo, can nourish and help recovery of the cells. The antidote for any poison can counter that poison. This Awareness indicates that while this is true, still, there are other factors in healing which do not depend strictly on the medicine involved, -- other factors which depend upon the attitude which is being administered along with the medicine. This Awareness indicates that the faith accompanied by the medicine is that which is the best combination. This Awareness indicates that the American Medical Association was made aware of the fact that faith was part of the healing process, and publicly announced this after an experiment whereby a certain medicine which had been used for healing a certain illness successfully for several years was proved to be absolutely worthless. The Medical Association had to acknowledge that the successes which occurred were the result of faith in medicine, rather than the medicine itself." [End of channelled reading]

[Note - The subconscious mind is your 'feeling mind', where you *feel* on all levels you want to live, which is far more powerful than at the conscious mind level where you have the thought 'I want to live'. In other words, your deep feelings on whether you want to live or not, deep down, have a greater affect on whether you continue to self-destruct or not, than simple conscious-level thoughts. The impression was given from Awareness during the channelled reading, that a person could jar the subconscious into reversing the self-destruct affirmation if the entity became so enraged, so indignant at the whole idea of dying from the death-wish, that he stomped on the floor, shouted and hollered, beat on the wall, and commanded his/her body to live, that these kind of activities, when repeated and repeated every day, were sufficient enough amplitude to cause a reversal of that message which had been telling the cells to self-destruct.]

[<http://cosmicawareness.org/96124.pdf>]

In my own personal experience in treating hundreds of cancer patients, the subconscious death wish is nearly always observable, and is linked to a high degree of unresolved psycho-emotional pain and burden. I present the following three cases each surrounding cancer of the breast, which according to Dr Ryke Geerd Hamer is either a "conflict concerning child, mother or home" [left breast] or "a conflict with partner or others" [right breast], occurring approximately 2 years prior to cancer diagnosis. The first case is my own mother who passed away from cancer of the left breast in 1997. She was highly-strung in nature and I remember her becoming hysterical and frantic on a number of occasions when she thought I was missing as a child. As mentioned previously, my mother's own mother passed away in 1990, which was the trigger event of her cancer manifesting two years later. They were very close and she mentioned to me at the time she felt like a zombie for months afterwards. Knowing my mother as I did, she was unprepared mentally and emotionally to bear the pain of loss of anyone she loved so dearly; she simply could not go on living with the pain in her heart she had no way of knowing how to heal. And this was confirmed when my sister saw a psychic medium not long after our mother's passing, and she told me our mother came through and revealed

the reason she got cancer was because of her mother's passing. [Note: At the time of my mother's passing I was her caregiver and not treating cancer patients.] In the second case I will present, a close family member Kim Perkinson who is happy to share her story, was diagnosed with cancer in 2008. I remember her telling me two years prior in 2006 of the pain of losing her two twin boys to the navy. These two boys were her world and she lived her life solely for them. I even had the intuitive thought given to me by God at the time, "you're going to end up with cancer". Two years later she was diagnosed with cancer of the left breast and began a program with myself to heal the emotional cause of her cancer. The pain that surfaced during these sessions of losing her boys was so great she could barely even speak about it. She communicated to me she simply did not want to go on living without her boys by her side. With gentle coaxing Kim was able to face and heal the pain of losing her boys and overcome her wanting to die and refocus on rebuilding her life for herself and her daughter. Since then she has trained as a theta healer and is a motivational speaker for empowering women to overcome cancer and adversity in their life. The third and final case I will present is of a well-known doctor, Dr Cherie Santasiero, founder, CEO and President of the Sedona Holistic Medical Centre in New York, who is also happy to share her story. Dr Santasiero contacted me in early September 2013 wanting to heal the psycho-emotional cause of her cancer, a rare and aggressive form of cancer, metaplastic carcinoma, of the right breast. We undertook the four 2-hour sessions on September 23 to 26, using visualization, regression therapy and EFT as the primary healing modality. Dr Santasiero presented with a high degree of unresolved psycho-emotional pain [typical of those with cancer] and communicated the fear / pain she felt around being left alone was so great [should her husband ever pass away before her] that she had mentally decided to die before her husband to prevent being left alone. During the sessions we were able to successfully heal all of the observable psycho-emotional pain and Dr Santasiero was able to face and heal the pain and fear around being left alone and the associated death wish. On October 14, two and a half weeks later, I received the following email: "Hi Glen, I wanted you to know that my last tests, CT scan, Mammo and MRI all showed up clear! The doctor was a bit surprised, but we were not. I have to be re-tested in three months. I will keep you posted. Thank you so much for all your help. I am learning EFT for my own family, friends and my patients. Take care and God bless, Cherie."

While the concept that cancer being caused by stress and unhealed emotions is relatively new, and as such many are unable to fathom or accept it, the concept that cancer is caused by a subconscious wanting to die is even more unpalatable. Many simply do not want to accept the premise they have created cancer within their body and prefer to believe it is a random event or is caused solely by other environment factors or is an act of God. Below is further evidence from God's angels which reveals cancer is indeed caused by a subconscious wanting to die.

God's Angels: "Today we begin our conversation and hope to help others by shedding a little light, from a spiritual perspective, on cancer. We are part of the spiritual force; when you give us your thoughts, desires, worries, troubles, we hear them. We are like the in-between you, and God. Some people call us their angels or guides. We are a collective that wish to deliver understanding to those in need at this time. There is an opportunity for some of you to grow spiritually and evolve. We wish to show some of you how to do this. We understand that cancer is a topic that is hotly contested. It is a sore point for humanity and there is much misunderstanding about why you have this, why you endure this and how you can help to create lives around, through, with, and get over this illness. So, let us begin. Cancer is a mechanism that is natural within the body. It is not an ogre or a demon. It has not been sent to humanity as a punishment. It is simply a mechanism within the body that rises and falls; as blood sugar rises, as blood sugar falls. The body is designed for this. The body understands that it moves from peaks to troughs in order to find its own homeostasis (balance). When cancer takes hold and forms what you would call 'a mass' there has been a break in the homeostasis of the body: there has been a rising without the fall. Our hope and belief is that each of you, as you read this information, will take away something that will help you return to balance. That may even provide you with a breakthrough to help your body achieve better levels of this homeostasis that we speak about.

Understanding that the body simply moves in cycles is crucial. There will be risings and falls in every system. There are days when you can be said to have cancer or days when you can be free of cancer; that you will feel better in body and feel worse in body. There are days where muscles work better and muscles work less whether you have had a diagnosis or not. This is simply the process of homeostasis. We say that the body can always comeback [from cancer]; it is just



a matter of extent. The body itself requires you to do one thing: Listen to its needs. And here is where the problem arises. Here is why we speak on this matter. To summarize the entire contents of this message in one sentence: you as a species have become devoid of your bodies, if we could say one thing to you is, "Get back into your bodies!" So, how do you do this? Where have you gone? The answer, in your language, is into your heads.

We ask you to ascertain: Are you in this life? You can only do that by being, firstly, within your body – being in your life. You can't escape it until you leave it, unless you move into your mind, the head, and this is the first mechanism of death. It is a statement to your spirit that you wish to leave. Now this may not be your intention. Your intention might simply be that you want to have a better car, to be richer, to be wiser, to be thinner, to be more youthful, to be stronger. What is mis-understood is that often, if these desires do not come from within [your soul] they activate the first part of your defense mechanism against living, which is exiting life. There are those for whom the exit clause is a stronger pull than the living clause. You see, understand that when the body has manifested its first defense against living there is a strength of connection towards the exit, so the strength of connection towards living needs to at least match that. This can be determined by, in some cases, the progression of the illness. For some it is a train that cannot be stopped and, they blame the body, they blame the medication, but really the connection to the exit is too strong. For many of these people, those are the people who simply accept the situation and understand that the end is nigh.

For others, the change in the body, the diagnosis, the connection to the exit is enough for 'a wake up', an opportunity to have a personal revolution and for some this will mean that conventional treatment will be effective, for the 'wake up' has occurred and the connection to life has been re-established. These people, these individuals, may in their choices choose other means too, alternative means, natural means. The means of recovery is not what is important; it is the strength of connection to living and to exiting. We would prefer to use "exit" rather than "death", for there is no death, there's only death of a temporary form, so we will continue to use "exit". Lots of you think that your body has hurt you, your body has abandoned you, some of you may think that spirit has hurt you, spirit has abandoned you. There can be no abandoning from spirit; we are always right beside you and we are at the end of every exit. We wish you to understand that cancer seems to hit hardest those of you who are devoid of the reality of life - which is birth, living and death. And this is important, for it is usually those who have become lost in [earthly] life - i.e. they live in their heads - that can be hit with cancer. You are eternal and your life here is temporary. So there is a forgetting of your eternal spiritual nature and often a diagnosis such as cancer gives you an opportunity to remember that this [earthly life] is only partly real.

Bodies, however, can get tired. So, the real question is for all of you.... Will you, in life, wake up to yourself? Waking up to yourself in life means honoring the form you have; honoring the wishes and desires that are truly yours – not your parents, not society's, not your peer groups. Will you allow yourself to live whilst alive? Or will you remove yourself from your reality and create a life that has no nourishment for you in it. This is a punishment for the body and the body will simply respond with consequence. For you, through your choices, may make it impossible for the body to restore its balance. You may switch off, without realizing it, the bodies homeostasis. The physical death that many of you are fearful of, we prefer to call exiting, as we have explained before. But fear of death can be fear of death of form, of status, of job, of partner, of wealth, of funding, of size, we could go on. This fear of death of form in the physical world leads to a fear of life. It is a question that everyone who is given the diagnosis of cancer should ask themselves. For being fearful of life opens up the connection to exit.

So, what is being fearful of forms of life? It is simply an expression of being devoid of an authentic connection to self. For if you are fearful of losing something which is outside of yourself, e.g. many people fear losing their homes, their jobs, etc. What happens if someone does lose their home? The mind equates this loss with death, yet the body will not die. The mind equates this fear of losing career with death, yet the body will not die. However, a connection is opened up [to death], for effectively it is what you are choosing. Put enough fears together and you will affect your functioning. The body will become heightened, unable to relax, unable to have pleasure for itself. When this happens, over time the body will become tired. Whilst this is an experience that the body can have, it is meant for short periods of time only. It is a matter of the body in heightened states for [long] periods of time that it was not designed for – therefore it is unable to return to its balance. This is what perpetual states of fear produce within the body. These states start off as more minor imbalances; more minor in that they may affect the digestive organs, they may affect the skin, certainly the cognitive functioning and the ability to hold focus. It takes a lot to manifest a mass that you would call cancer.

Do you know that many of you do not know how to live? What life is equated with, is an automatic functioning which feels like a death of the spirit. It is an alarm clock in the morning, a shower followed by something to eat, followed by a hard day at the office, followed by television, alcohol and then rest. This is life of a sort, but living in its fullest extent is the enfoldment of self into the physical environment. This can happen through enjoyment, but most importantly this can happen through connection to everything in life. It means switching off autopilot. Hear your alarm; if you don't like it choose another one. If you hate it, go to bed earlier so you can wake without one. It is about engaging with everything that is before you and assessing: (Do I really want this in my life?)” Similarly, be aware of everything you choose to expose yourself to. You are a sensory being. You have your five senses. Yet many people expose themselves to sensory material that is fashionable rather than allows the spirit to unfold and enjoy itself in. There was once a movement, backed by us for obvious reasons that encouraged the enfoldment of spirit through “love”, “beauty” and “truth”. We think it is time for this again. If you don't like the fact that the mechanism to take you to your exit has kicked off, connect to the opposite side, which is life. There are times in life where you are given bad news or bad life events happen to you; by ‘bad’ we mean that which you wouldn't choose consciously. But recognize this is part of the process of learning to be a happy, healthy, balanced human being. Remember that you have not exited yet and for as long as there is life within, you are life itself, so live.

The best thing about cancer is that it shouts loudest of all: wake up! What ‘life’ means to an individual at one time can be different from the next time. Connect with who you are at that time and give yourself what it is you need. Recognize though, that if you have opened the mechanism to exit, you have not been giving yourself what you need for a sustained time. There must be at least as many connections to life, at least, as there was to the mechanism that kicked off the exit. Many give up on this and think: I'll do this, I'll do this, and I'll do this. Oh look, the Drs told me that I'm still dying. The reality is that you are dying anyway (everyone is). You only have one exit. But you can be in charge of the quality of how you live while you are alive, and this may be enough to disable the mechanism towards the exit. What [individuals diagnosed with cancer] fail to understand is that they have taken away life from themselves and the body simply responded. Understand that the body did not let you down; neither did you deliberately choose cancer. There was something happening in your life to the point of diagnosis, and perhaps to this point today, that opened up the mechanism for exit.”

[<http://spiritual-light-on-cancer.blogspot.co.nz/>]

The decision to exit life occurs in stages for those diagnosed with cancer. Prior to the formation of cancer in the body, the cancer personality experiences a psycho-emotional trauma usually occurring 2-3 years prior to cancer diagnosis. This is akin to the straw that breaks the camel's back, for the cancer personality is usually already highly stressed before this event, and when faced with the trauma of this final inescapable psycho-emotional shock, the homeostasis (or balance) of the will to live versus the will to exit is tipped in balance in favour of the will to exit. This final event causes a feeling of hopelessness and helplessness, depleting serotonin and dopamine levels in the brain, causing internal depression. The inner feeling of depression and hopelessness and unresolved psycho-emotional pain sponsors the subconscious wanting to exit life. When an individual makes a decision to exit life, subliminal thoughts are sent to the immune system to shut down and stop production of interleukin-2-producing T cells, B cells, natural killer cells, macrophages and neutrophils. Without immune system cells, viral-bacterial-yeast-like-fungus that have pleomorphised within cells continue to grow and newly created cancer cells continue to multiply. The news of cancer becomes a further inescapable shock and further evidence that life is too hard, too overwhelming and too painful and in many cases reinforces the already existing subconscious wanting to die, resulting in metastasis.

The Holy Spirit of God: "This Awareness indicates that cancer as being a psychic disease brought on by a type of death-wish wherein entities wish to escape certain levels of involvement in life, is that which can be cured both through psychic healing [of mind and the emotions], as well as through certain physical methods. This Awareness suggests that often this is a subconscious death-wish, being that which is of a feeling level on certain levels that are not purely rational. This Awareness indicates this often comes in feelings of being rejected or alienated from another, often through the loss of a loved one, whether this loss be through death, departure, or rejection. This Awareness indicates that the death-wish often approach entities some time after this loss, the average time being approximately three years for the cancer situation to begin having its effect. This Awareness suggests that wherein an entity does have cancer of any kind, that the first step toward healing is to check yourself to discover if you might have a subconscious death-wish, and in this checking, to move back to two, three, or four years in your life, examining experiences wherein you may have felt a loss, an alienation, or a rejection that caused you to feel like giving up as though the question were asked, "What is the use of living?". This Awareness indicates that this attitude becomes the triggering attitude that leads to the subconscious death-wish which helps to bring on diseases such as cancer."

[<http://cosmicawareness.org/16506.pdf>]

Within the 6<sup>th</sup> Phase of Cancer the following sequence of events can be observed in the cancer patient:



## The Evidence

The evidence for Phase 6 of Cancer can be broken down into the following components: a) the link between high stress hormone cortisol levels and depleted serotonin levels, b) the link between serotonin receptors stimulating dopamine release in the brain, c) the link between depleted serotonin levels, reduced dopamine levels and the onset of depression, d) the link between depleted dopamine levels and cancer, e) the link between cancer and inescapable shock, learned helplessness and depression, f) the link between the mind and immune system responsiveness, g) the link between suicidal / depressive thoughts and suppressed immune system function, h) the link between suppressed immune system function and increased viral-bacterial-fungal infection [in patients with and without cancer].

### ➤ Evidence of the Link Between High Stress Hormone Cortisol Levels and Depleted Serotonin Levels

231. The Touch Research Institutes, University of Miami School of Medicine, found massage used to reduce stress cortisol levels significantly increased serotonin levels: "In this article the positive effects of massage therapy on biochemistry are reviewed including decreased levels of cortisol and increased levels of serotonin and dopamine. The research reviewed includes studies on depression (including sex abuse and eating disorder studies), pain syndrome studies, research on auto-immune conditions (including asthma and chronic fatigue), immune studies (including HIV and breast cancer), and studies on the reduction of stress on the job, the stress of aging, and pregnancy stress. In studies in which cortisol was assayed either in saliva or in urine, significant decreases were noted in cortisol levels (averaging decreases 31%). In studies in which the activating neurotransmitters (serotonin and dopamine) were assayed in urine, an average increase of 28% was noted for serotonin and an average increase of 31% was noted for dopamine. These studies combined suggest the stress-alleviating effects (decreased cortisol) and the activating effects (increased serotonin and dopamine) of massage therapy on a variety of medical conditions and stressful experiences." [<http://www.ncbi.nlm.nih.gov/pubmed/16162447>]
232. In a study conducted by the Weizmann Institute of Science, Israel, researchers found a direct link between elevated stress hormone cortisol levels and serotonin suppression. "In the present work we investigated the cortisol-induced increase in serotonin uptake in cell lymphocytes from hypercortisolemic patients, including subjects with major depressive disorder (n = 8), and subjects with generalized anxiety disorder (n = 12), in comparison with a control group of normal healthy subjects (n = 8). A significant increase in serotonin uptake (+37% + 14, M + SD) was observed in the control group, whereas neither the generalized anxiety disorder nor the major depression group exhibited changes in serotonin uptake upon incubation with cortisol. It is likely that under chronic stress or depression, the capacity for increase in serotonin transporter has reached its limit due to the chronically elevated blood cortisol level." [<http://www.ncbi.nlm.nih.gov/pubmed/12467090>]
233. The Intramural Research Program, Clinical Brain Disorders Branch / National Institute of Mental Health, USA, found a direct link between high stress hormone cortisol levels and reduced serotonin transporter availability in alcoholics. "The availability of serotonin transporters was measured with [<sup>125</sup>I]-beta-CIT and SPECT in the raphe area in brainstem in 31 alcoholics after four weeks of abstinence and in 25 age-matched healthy volunteers. Among male alcoholics and healthy volunteers, CSF 5-HIAA (serotonin metabolic levels) and plasma cortisol concentrations were inversely correlated with the availability of raphe serotonin transporters and positively correlated with the severity of clinical depression. Our findings support the hypothesis of an interaction between reduced serotonin transporters, stress hormone activation and clinical depression. The observed interactions between high cortisol concentrations and reduced serotonin transporter availability warrant further studies in major depression and other neuropsychiatric diseases with implied cortisol activation and serotonergic dysfunction." [<http://www.ncbi.nlm.nih.gov/pubmed/12163982>]
234. The Department of Biochemistry, Central Institute for Mental Health, Germany, studied rats exposed to stress conditions and found an immediate link between high stress hormone cortisol levels and reduced serotonin production capability. "The aim of the current study was to investigate the effect of acute immobilization stress on the expression of serotonin transporter (SERT) mRNA (molecules) in the raphe nuclei as a parameter of serotonergic innervation (serotonin stimulation). We have examined the expression of SERT mRNA and of BDNF (brain-derived neurotrophic factor) mRNA in rats upon acute immobilisation by quantitative in situ hybridisation with a (<sup>35</sup>S)-labelled oligonucleotide probe. Elevated corticosterone (cortisol) levels in stressed animals confirmed as internal controls the effect of stress under our conditions. Acute stress led to a significant decrease of BDNF mRNA in the hippocampus and of SERT (serotonin transporter) mRNA in the raphe pontis. These data provide evidence for fast interactions between neurotrophins, corticosterone and serotonergic neurotransmission under stress conditions." [<http://www.ncbi.nlm.nih.gov/pubmed/10936689>]

235. In a study conducted by the Division of Reproductive Sciences, Oregon National Primate Research Center researchers found highly stressed monkeys had lower serotonin gene expression. "In this study, the expression of four genes pivotal to serotonin neural function was assessed in monkeys previously categorized as highly stress resistant, medium stress resistant, or low stress resistant. In situ hybridization and quantitative image analysis was used to measure mRNAs coding for SERT (serotonin transporter), 5HT1A (serotonin) auto-receptor, MAO-A and MAO-B (monoamine oxidases) at six levels of the [brain] dorsal raphe nucleus (DRN). Stress sensitive animals had lower expression of SERT (serotonin transporter) mRNA in the caudal region of the [brain] DRN. 5HT1A (serotonin) mRNA OD signal tended to decline in the stress-sensitive group. There was significantly less MAO-A mRNA signal in the stress-sensitive group. MAO-B mRNA exhibited a similar downward trend in the stress-sensitive group. Thus, all serotonin-related mRNAs examined in the [brain] dorsal raphe to date were lower (SERT, MAO-A) or exhibited a lower trend (5HT1A, MAO-B) in the stress sensitive animals." [<http://www.ncbi.nlm.nih.gov/pubmed/15780474>]

➤ Evidence of the Link Between Serotonin Receptors Stimulating Dopamine Release in the Brain

236. In a study conducted by the Department of Psychiatry, Wayne State University School of Medicine, Detroit, researched confirmed serotonin's vital role in stimulating dopamine release to counteract depression. "Using microdialysis, changes in extraneuronal levels of dopamine (DA), and the metabolites of DA (dopamine) and serotonin (5-HT), were monitored concurrent with perfusion of 5-HT1 (serotonin) agonists into the anterior [brain] striata of anesthetized rats. Perfusion of 5-HT (serotonin) facilitated DA (dopamine) release in a dose dependent manner, and to a greater extent than any other agonist tested. Extraneuronal DA (dopamine) levels increased 34% with perfusion of 0.04 nmol 5-HT (serotonin) and 18-fold with perfusion of 4.0 nmol 5-HT (serotonin)." [<http://www.ncbi.nlm.nih.gov/pubmed/1769366>]

237. The Department of Psychiatry, Yale University School of Medicine, Connecticut, confirmed serotonin's vital role in regulating the release of dopamine to counteract depression. "5-HT (serotonin) in concentrations of 1 to 10 microM increased extracellular DA (dopamine) dose-dependently to a greater extent in the [brain] PFC (prefrontal cortex) than in the striatum. The results obtained demonstrate a functional interaction between DA (dopamine) and 5-HT (serotonin) pathways in the PFC (prefrontal cortex), with evidence of potential mediation by the 5-HT1B (serotonin) receptor subtype." [<http://www.ncbi.nlm.nih.gov/pubmed/8613947>]

238. The Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York, also confirmed serotonin's role in regulating the release of dopamine to counteract depression. "Modulation of [brain] striatal dopamine (DA) release by serotonin (5HT) and its antagonists was studied utilizing in vitro perfusion techniques. In isolated [brain] striatal tissue, 5HT (10 microM serotonin) increased the fractional basal release of labeled DA (dopamine). These results indicate that 5HT (serotonin)-mediated DA (dopamine) release occurs via reversal of the DA (dopamine) transporter and that inhibitory presynaptic 5HT (serotonin) heteroreceptors and both inhibitory and stimulatory somato-dendritic 5HT (serotonin) receptors regulate release." [<http://www.ncbi.nlm.nih.gov/pubmed/11113592>]

239. In a study conducted by the Université de Bordeaux II, France, researchers found serotonin increased the release of dopamine levels in rats significantly. "Serotonin (5-HT) applied at 1, 3, and 10 microM into the striatum of halothane-anesthetized rats by in vivo microdialysis enhanced dopamine (DA) outflow up to 173, 283, and 584% of baseline values, respectively. These results show that striatal 5-HT4 (serotonin) receptors are involved in the 5-HT (serotonin)-induced enhancement of striatal DA (dopamine) release in vivo and that they are not located on striatal DA (dopamine) terminals." [<http://www.ncbi.nlm.nih.gov/pubmed/8978726>]

➤ Evidence of the Link Between Low Serotonin Levels, Reduced Dopamine Levels and the Onset of Depression

240. In a study conducted by the Department of Neurosurgery, Faculty of Medicine, University of Sherbrooke, Canada, researchers found patients with major depressive disorder had significantly lower serotonin levels than non-depressive controls. "Twenty-nine FM (fibromyalgia) patients, 17 MDD (major depressive disorder) patients, and 57 HC (healthy controls) were recruited who did not differ in terms of age, sex, and the presence or absence of a regular menstrual cycle. Plasma samples were analysed with mass spectrometry. Serotonin levels were decreased in MDD (major depressive disorder) patients, relative to FM (fibromyalgia) patients and HC (healthy controls)." [<http://www.ncbi.nlm.nih.gov/pubmed/21415718>]

241. A study conducted by the Department of Psychological Medicine, Institute of Psychiatry, London, revealed patients with major depression had significantly lower serotonin levels. "Whole blood serotonin (WBS) was measured in 17 patients with DSM-III-R major depression and compared to a healthy control group of 57.

Values were significantly lower in the depressed group, but there was no correlation with the degree of depression. Four patients with a history of suicide attempts had even lower levels, but this was not statistically significant." [<http://www.ncbi.nlm.nih.gov/pubmed/9262942>]

242. A study conducted by the Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, revealed patients with bi-polar depression had significantly lower serotonin levels than healthy controls. "A sample of 18 medication-free patients with bipolar depression and 41 controls [were included in the study]. Patients with bipolar disorder had 16% to 26% lower serotonin transporter BP(1) in the midbrain, amygdala, hippocampus, thalamus, putamen, and anterior cingulate cortex. Lower serotonin transporter BP(1) in bipolar depression overlaps with that observed in major depression and suggests that serotonergic dysfunction is common to depressive conditions." [<http://www.ncbi.nlm.nih.gov/pubmed/17283287>]
243. In a groundbreaking study, the Department of Psychopharmacology, Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Psychiatric Hospital Vrapce, University Department of General and Forensic Psychiatry and Clinical Psychophysiology, Zagreb, Croatia, found suicidal patients [with or without post traumatic stress disorder] had significantly lower serotonin levels than control subjects. "Posttraumatic stress disorder (PTSD) is a serious and global problem, a psychiatric disorder that frequently occurs with different comorbidities, and is associated with a high suicide rate. Pathophysiologically, both PTSD and suicidal behavior are related to disturbances in the central serotonergic system. Serotonin (or 5-HT) controls emotional behavior, anxiety, impulsivity and aggression, and nearly all known antidepressants and anti-anxiety drugs affect 5-HT transmission. This study examined platelet 5-HT (serotonin) concentration by the spectrofluorimetric method in male subjects: 73 suicidal and 47 non-suicidal veterans with current and chronic combat related PTSD, 45 suicidal and 30 non-suicidal comparative non-PTSD subjects and 147 healthy men. Platelet 5-HT (serotonin) concentration was significantly lower in suicidal (PTSD and non-PTSD patients) compared to non-suicidal patients or healthy controls." [<http://www.ncbi.nlm.nih.gov/pubmed/18055084>]
244. In a 1976 study conducted by Takahashi S of Japan, depressed patients had significantly lower serotonin levels than healthy controls. "Blood platelet serotonin levels were measured in unmedicated 12 manic and 74 depressive patients with 118 normal control subjects employed. The mean value of blood platelet serotonin levels in depressed patients was 594 +/- 288 ng/mg platelet protein (+/- S.D.), which was significantly lower than that for normal controls, 780 +/- 253 ng/mg protein. Unipolar (deeply sad) and involuntional (highly agitated) depressed patients exhibited to have the most pronounced reduced levels of serotonin of various subtypes of depression." [<http://www.ncbi.nlm.nih.gov/pubmed/1021543>]
245. In a study conducted by the Department of Clinical Physiology, Sahlgrenska University Hospital, Sweden, researchers found depressed patients had significantly lower dopamine levels than healthy control subjects. "In accordance with the monoamine hypothesis, a deficit in brain norepinephrine and dopamine exists in patients with depressive illness. Paradoxically it was the brain's turnover of dopamine that bore a significant relation to the patients' clinical status ( $r(s) = 0.79$ )." [<http://www.ncbi.nlm.nih.gov/pubmed/10920468>]
246. The Division of Clinical and Biological Research, National Institute on Alcohol Abuse and Alcoholism, Maryland, USA, found depressed suicidal patients had significantly lower serotonin and dopamine levels. "We carried out a 5-year follow-up study of suicidal behavior among depressed patients who earlier had determinations of cerebrospinal fluid levels of monoamine metabolites. Patients who reattempted suicide during the follow-up had significantly lower cerebrospinal fluid levels of both the serotonin metabolite 5-hydroxyindoleacetic acid and the dopamine metabolite homovanillic acid. The findings were most striking among melancholic patients. These follow-up results suggest that reduced central turnover of serotonin and dopamine may be associated with further suicidal behavior among depressed patients who have previously attempted suicide." [<http://www.ncbi.nlm.nih.gov/pubmed/2472124>]
247. In a study conducted by the Department of Neurology, Boston University School of Medicine, Massachusetts, researchers found patients with neuropsychological defects including major depression had lower levels of the dopamine metabolite Homovanillic acid (HVA). "A distinct pattern of neuropsychological deficits was associated with low [dopamine] homovanillic acid (HVA) [levels] in the cerebrospinal fluid of 21 patients with: Alzheimer's disease (9), Parkinson's disease (8) and major depressive disorders (4). Regardless of clinical diagnosis, patients with low [dopamine] HVA (homovanillic acid) [levels] were slower on a test of efficiency of processing timed information, and showed greater benefit from semantic structure on a verbal fluency task. Across three diagnostic groups, patients with lower [dopamine] HVA (homovanillic acid) [levels] also tended to have more extrapyramidal motor signs and were significantly more depressed. These results demonstrate a

significant relationship between specific neuro-behavioural deficits and dopaminergic activity which cuts across traditional diagnostic categories.” [http://www.ncbi.nlm.nih.gov/pubmed/2266376]

248. In a study conducted by PET Imaging Centre, and Mood Division, Centre for Addiction and Mental Health, Department of Psychiatry and University of Toronto, researchers found: “Previous studies suggest that there is a dopamine lowering process during major depressive episodes (MDE). To investigate this, we measured the dopamine transporter binding potential (DAT BP) in the [brain] striatum of depressed and healthy subjects using [(11)C]RTI-32 PET. The DAT, a predominantly presynaptic [dopamine] receptor, decreases in density after chronic dopamine depletion and the BP is proportional to receptor density. In all striatal regions [of the brain], subjects with MDE (major depressive episodes) had significantly lower DAT BP (dopamine transporter binding potential).” [http://www.ncbi.nlm.nih.gov/pubmed/11742250]
249. In a study conducted by the Clinic of Nuclear Medicine, University Hospital Düsseldorf, researchers found a deficiency in dopamine, serotonin and the amino acid GABA were central to mood and anxiety disorders. “On a total of 504 patients with obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), panic disorder (PD), phobia, or posttraumatic stress-disorder (PTSD) and 593 controls, investigations of VMAT2 (dopamine and serotonin transporter protein), DAT (dopamine transporter), SERT (serotonin transporter), D1, D2 (dopamine receptors), 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, (serotonin receptors) GABA(A), and NK1 (natural killer cell) receptor binding in neostriatum, ventral striatum, thalamus, neocortex, limbic system, cingulate, midbrain/pons or cerebellum were performed. Pooling of all disorders yielded a significant reduction of mesencephalic SERT (serotonin transporter) (-13%), mesencephalic (-27%) as well as cingulate 5-HT<sub>1A</sub> (serotonin) receptors (-18%), striatal [brain] D2 (dopamine) receptors (-21%) and frontal (-14%), temporal (-14%), occipital (-13%) and cingulate GABA<sub>A</sub> receptors (-15%). The results show that DA (dopamine), 5-HT (serotonin), and GABA play a major role in all subtypes of anxiety disorders. In particular, the findings imply that the regulation state of DA (dopamine) as modulated by GABA and 5-HT (serotonin) may be crucial for the development of anxiety- and compulsion-related disorders.” [http://www.ncbi.nlm.nih.gov/pubmed/20614802]

➤ Evidence of the Link Between Depleted Dopamine Levels and Cancer

250. The Departments of Gynecologic Oncology, Cancer Biology, and Experimental Therapeutics, and Center for RNA Interference and Non-coding RNA, University of Texas MD Anderson Cancer Center, conducted a study on animals to determine the relationship between dopamine and cancer. “The focus of the current study was to determine whether dopamine, an inhibitory catecholamine, could block the effects of chronic stress on tumor growth. In this model of chronic stress, tumoral norepinephrine levels remained elevated whereas dopamine levels were significantly decreased compared with nonstressed animals. Daily restraint stress resulted in significantly increased tumor growth in both immunodeficient and immunocompetent ovarian cancer models. This increase [in tumor growth] was completely blocked with daily dopamine treatment. Dopamine treatment also blocked the stress-induced increase in angiogenesis [which is the formation of blood vessels that cause metastasis]. DR2 (dopamine receptor) was responsible for the inhibitory effects of dopamine on tumor growth and microvessel density as well as the stimulatory effect on apoptosis (tumor cell death), as the DR2 antagonist eticlopride reversed these effects. Dopamine significantly inhibited [tumor] cell viability and stimulated apoptosis in vitro. Moreover, dopamine reduced cyclic AMP levels and inhibited norepinephrine and vascular permeability factor/VEGF-induced Src kinase activation. Dopamine depletion under chronic stress conditions creates a permissive micro-environment for tumor growth that can be reversed by dopamine replacement.” [http://www.ncbi.nlm.nih.gov/pubmed/21531818]
251. The Department of Gynecologic Oncology, The University of Texas MD Anderson Cancer Center, conducted a further study on mice with ovarian cancer and found: “Exogenous administration of DA (dopamine) not only decreased tumor microvessel density but also increased pericyte coverage of tumor vessels following daily restraint stress in mice. DA (dopamine) treatment blocked stress-mediated increases in tumor growth and increased pericyte coverage of tumor endothelial cells. In conclusion, DA (dopamine) stabilizes tumor blood vessels through activation of pericyte cAMP-protein kinase A signaling pathway by [dopamine receptor] DR1. These findings could have implications for blocking the stimulatory effects of chronic stress on tumor growth.” [http://www.ncbi.nlm.nih.gov/pubmed/23633922]
252. In a study conducted by the Department of Molecular Sciences, The University of Tennessee Health Science Center, researchers found dopamine receptors inhibit small cell lung cancer cell growth. “The D2 dopamine receptor agonist bromocriptine [a chemical receptor binding agent] has been used clinically for reducing tumor mass of pituitary adenomas arising from lactotroph origins. The activation of the D2R (dopamine receptor) results in an inhibition of growth of NCI-H69 (small lung cancer) cells. In NCI-H69 cells, the D2

dopamine-like receptor is coupled to the inhibition of forskolin-stimulated cAMP accumulation and to the stimulation of phospholipase D. These data suggest that the phospholipase D pathway is responsible for the antiproliferative effects of D2 dopamine-like receptors agonists in small cell lung cancer cells. In support of this hypothesis, the inhibition of [(3)H]thymidine incorporation mediated by dopaminergic agonists was shown to be sensitive to the presence of ethanol. Taken together, these data suggest that the D2 dopamine-like receptor activates phospholipase D, which ultimately leads to an inhibition of growth of this small cell lung cancer cell line." [<http://www.ncbi.nlm.nih.gov/pubmed/17581302>]

253. The Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, found women who had taken an antipsychotic drug which reduced dopamine production had a significantly increased risk of breast cancer. "A retrospective cohort study was conducted of 52 819 women exposed and 55 289 not exposed to dopamine antagonists [a drug which blocks dopamine receptors and thus dopamine production] between January 1, 1989, and June 30, 1995. Use of antipsychotic dopamine antagonists was associated with a 16% increase in the risk of breast cancer, with a dose-response relationship between larger cumulative dosages and greater risk." [<http://www.ncbi.nlm.nih.gov/pubmed/12470131>]
254. In a study conducted by the Signal Transduction and Biogenic Amines Laboratory, India, researchers found dopamine significantly increased the effects of anti-cancer drugs. "The effect of dopamine was investigated in human breast cancer-(MCF-7) and colon (HT29) cancer-bearing mice. Dopamine, in combination with anticancer drugs, significantly inhibited tumor growth and increased the life span when compared with treatment with dopamine or anticancer drugs alone. The antiangiogenic action of dopamine was mediated by inhibiting proliferation and migration of tumor endothelial cells through suppression of VEGF receptor-2, mitogen-activated protein kinase, and focal adhesion kinase phosphorylation. Our study shows that dopamine significantly enhances the efficacies of commonly used anticancer drugs and also indicates that an inexpensive drug like dopamine...might have a role as an antiangiogenic agent for the treatment of breast and colon cancer." [<http://www.ncbi.nlm.nih.gov/pubmed/18413843>]
255. The International Agency for Research on Cancer, Lyon, France found disruption in dopamine receptor genes was associated with a significant risk in non-small lung cancer. "The dopaminergic pathway may be of interest in assessing risk of non-small cell lung cancer. Dopamine receptors are expressed in alveolar epithelial cells and human lung tumours, and dopamine inhibits both cell proliferation in vitro and growth of lung tumour xenografts in nude mice. Moreover, dopamine selectively inhibits the vascular permeability and angiogenic activity of vascular endothelial growth factor (VPF/VEGF). The bioavailability of dopamine is regulated by dopamine receptors D2 (DRD2), D4 (DRD4) and dopamine transporter 1 (DAT1/SLC6A3) genes. We have analysed 10 single nucleotide polymorphisms (disruptions) in DRD2, DRD4 and DAT1/SLC6A3 (dopamine receptor) genes in relation to lung cancer risk in a case-control study of smoking subjects. The study subjects were 413 healthy individuals from general population and 335 NSCLC (non-small cell lung cancer) cases. We demonstrate that DRD2 (dopamine receptor) polymorphisms (disruptions) are associated with a two- to five-fold increased NSCLC risk. The data show that the polymorphisms resulting in lower dopamine bioavailability were associated with increased risk of NSCLC." [<http://www.ncbi.nlm.nih.gov/pubmed/17175058>]
256. The Signal Transduction and Biogenic Amines Department, Chittaranjan National Cancer Institute, India conducted a study and found dopamine inhibits gastric cancer cell proliferation. "The overexpression of insulin-like growth factor receptor-I (IGF-IR) and the activation of its signaling pathways both play critical roles in the development and progression of gastric cancer. We have previously reported that both DA (dopamine) and tyrosine hydroxylase, the rate-limiting enzyme required for the synthesis of DA (dopamine), are lost in malignant gastric tissues. To determine whether this loss of DA (dopamine) has any effect on the activation of IGF-IR signaling pathways in malignant gastric tumors, in vitro experiments were undertaken, using AGS gastric cancer cells. Our results demonstrated that DA (dopamine) acting through its D(2) receptor, inhibits IGF-I-induced proliferation of AGS cells by up-regulating KLF4, a negative regulator of the cell cycle through down regulation of IGF-IR and AKT phosphorylation. Our results suggest that DA (dopamine) is an important regulator of IGF-IR function in malignant gastric cancer cells." [<http://www.ncbi.nlm.nih.gov/pubmed/21075859>]
257. In a study conducted by the Department of Biochemistry and Molecular Biology and Mayo Clinic Cancer Center, researchers found mice depleted of dopamine had a significantly higher tumor growth factor, known as vascular endothelial growth factor. "We report here that ablation (removal) of peripheral dopaminergic nerves markedly increased angiogenesis [the formation of blood vessels that causes metastasis], microvessel density, microvascular permeability, and growth of malignant tumors in mice. Endogenous peripheral dopamine acted through D2 (dopamine) receptors, as significantly more angiogenesis and tumor growth was



observed in D2 dopamine receptor knockout mice in comparison with controls. The vascular endothelial growth factor (VEGF) receptor 2 phosphorylation, which is critical for promoting angiogenesis [leading to metastasis], was also significantly more in tumor endothelial cells collected from the dopamine-depleted and D2 dopamine receptor knockout animals. These results reveal that peripheral endogenous neurotransmitter dopamine might be an important physiological regulator of vascular endothelial growth factor (VEGF)-mediated tumor angiogenesis and growth." [<http://www.ncbi.nlm.nih.gov/pubmed/15313889>]

258. In a study conducted by the Departments of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, researchers found dopamine inhibited tumor mechanisms VEGF and VPF. "It has been shown that vascular permeability factor/vascular endothelial growth factor (VPF/VEGF), a potent cytokine expressed by most malignant tumors, has critical roles in vasculogenesis and both physiological and pathological angiogenesis [both of which are the formation of blood vessels causing metastasis]. We report here that at non-toxic levels, the neurotransmitter dopamine strongly and selectively inhibited the vascular permeabilizing and angiogenic activities of VPF/VEGF. Dopamine acted through D2 dopamine receptors to induce endocytosis (the engulfing) of VEGF receptor 2, which is critical for promoting angiogenesis, thereby preventing VPF/VEGF binding, receptor phosphorylation and subsequent signaling steps. The action of dopamine was specific for VPF/VEGF and did not affect other mediators of microvascular permeability or endothelial-cell proliferation or migration. These results reveal a new link between the nervous system and angiogenesis and indicate that dopamine and other D2 (dopamine) receptors, already in clinical use for other purposes, might have value in anti-angiogenesis therapy." [<http://www.ncbi.nlm.nih.gov/pubmed/11329058>]

➤ Evidence of the Link Between Cancer and Inescapable Shock, Learned Helplessness and Depression

259. Madelon Visintainer, now Associate Professor at Yale University School of Medicine, conducted a study in 1982 with Martin Seligman to determine whether inescapable shock / learned helplessness affected tumour growth in rats. "Rats experienced inescapable, escapable, or no electric shock 1 day after being implanted with a Walker 256 tumor preparation. Only 27 percent of the rats receiving inescapable shock rejected the tumor, whereas 63 percent of the rats receiving escapable shock and 54 percent of the rats receiving no shock rejected the tumor. These results imply that lack of control over stressors reduces tumor rejection and decreases survival." [<http://www.sciencemag.org/content/216/4544/437>]

260. The Department of Psychology, University of British Columbia reviewed 25 independent studies to determine whether depression affected mortality rates in those with cancer. "Based on data from 25 independent studies, mortality rates were up to 25% higher in patients experiencing depressive symptoms (RR unadjusted = 1.25; 95% CI, 1.12-1.40), and up to 39% higher in patients diagnosed with major or minor depression (RR unadjusted = 1.39; 95% CI, 1.10-1.89). [<http://www.ncbi.nlm.nih.gov/pubmed/19753617>]

261. In a study of 103 lung cancer patients conducted by the University of Würzburg, researchers found patients with a depressive coping style (helpless in attitude) had significantly shorter survival than patients who were hopeful and possessed an active coping style. "At follow-up, which took place three to five years later, n = 74 patients had died, for n = 29 patients the survival data are censored. Results were as follows: Active coping and hope were associated with longer survival, [while] emotional distress, depression and depressive coping with shorter survival, respectively. These associations were found consistently across assessment methods. The predictive effects of coping and distress were statistically independent of the influence of the somatic risk factors." [<http://www.ncbi.nlm.nih.gov/pubmed/9333831>] A 10 year follow-up of patients revealed: "A cohort of 103 patients newly diagnosed with cancer was followed for 10 years. In a survival analysis with adjustment for known biomedical prognostic factors such as tumor stage, histological classification, and Karnofsky performance status, a depressive coping style, assessed by patients' self-reports, was linked with shorter survival (relative risk=1.91), and an active coping style, as assessed by interviewers' ratings, was linked with longer survival (relative risk=0.72)." [<http://www.ncbi.nlm.nih.gov/pubmed/12450966>]

262. The National Institutes of Health conducted a landmark study involving 534 lung cancer patients to see whether pessimism affected mortality rates. "Survival time of 534 adults, who were diagnosed with lung cancer and had a pessimistic explanatory style, was examined. Patients who exhibited a non-pessimistic explanatory style survived approximately six months longer than patients classified as having a pessimistic explanatory style." [<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2854019/>]

263. A study of 578 women with early stage breast cancer conducted by the Royal Marsden Hospital NHS Trust was undertaken to see whether helplessness and depression affected mortality. "At 5 years, 395 women were alive and without relapse, 50 were alive with relapse, and 133 had died. There was a significantly increased

risk of death from all causes by 5 years in women with a high score on the HAD scale category of depression (hazard ratio 3.59 [95% CI 1.39-9.24]). There was a significantly increased risk of relapse or death at 5 years in women with high scores on the helplessness and hopelessness category of the MAC scale compared with those with a low score in this category (1.55 [1.07-2.25])." [<http://www.ncbi.nlm.nih.gov/pubmed/10533861>]

264. As reported by S. Greer: "A prospective, multidisciplinary, 5-year study of 69 consecutive female patients with early (T0,1N0,1M0) breast cancer was conducted. Patients' psychological responses to the diagnosis of cancer were assessed 3 months postoperatively. These responses were related to outcome 5 years after operation. Recurrence-free survival was significantly common among patients who had initially reacted to cancer by denial or who had a fighting spirit than among patients who had responded with stoic acceptance or feelings of helplessness and hopelessness." [<http://www.ncbi.nlm.nih.gov/pubmed/90871?dopt=Abstract>]

➤ Evidence of the Link Between the Mind and Immune System Responsiveness

265. A study conducted by the University of South Florida, College of Nursing, found the use of guided imagery increased immune responsiveness in breast cancer patients significantly. "This pilot study used a pretest-posttest experimental design with 28 breast cancer patients, aged 25 to 75 years, with the diagnosis of stage 0, 1, or 2 breast cancer. The experimental group received a relaxation and guided imagery intervention and the control group received standard care. The effects of the intervention on immune function were measured by natural killer (NK) cell cytotoxicity and IL-2 (interleukin 2)-activated NK cell activity prior to surgery and 4 weeks postsurgery. Significant differences between groups were found at 4 weeks postsurgery. T-tests showed increased NK cell cytotoxicity for the intervention group at 100:1, 50:1, and 25:1 effector cell: target cell ratios (E:T) and increased activation for IL-2 at 100:1, 50:1, 25:1, and 12.5:1 (E:T) for the intervention group as compared to the control group." [<http://www.ncbi.nlm.nih.gov/pubmed/18077773>]
266. In a study conducted by the United Lincolnshire Hospitals NHS Trust, United Kingdom, researchers found guided imagery mind intervention significantly increased immune response. "Eighty women undergoing multimodality treatment for large (>4cm) or locally advanced (T3, T4, Tx, N2), breast cancers participated in a randomised controlled trial (RCT) to evaluate the immuno-modulatory effects of relaxation training and guided imagery. Patients underwent chemotherapy followed by surgery, radiotherapy, and hormone therapy. Those in the intervention group were taught relaxation and guided imagery. Patients kept diaries of the frequency of relaxation practice and imagery vividness. On 10 occasions during the 37 weeks following the diagnosis, blood was taken for immunological assays CD phenotyping: T cell subsets (helper, cytotoxic), natural killer (NK) and lymphokine activated killer (LAK) cells, B lymphocytes and monocytes; cytotoxicity: NK and LAK cell activities; cytokines interleukin 1 beta, 2, 4 and 6 and tumour necrosis factor alpha. Significant between-group differences were found in the number of CD25+ (activated T cells) and CD56+ (LAK cell) subsets. The number of CD3+ T cells was significantly higher following chemotherapy and radiotherapy, in patients randomised to relaxation and guided imagery. Using a median split, women who rated their imagery ratings highly had elevated levels of NK cell activity at the end of chemotherapy and at follow-up. Significant correlations were obtained between imagery ratings and baseline corrected values for NK and LAK cell activity, and IL1beta. Relaxation frequency correlated with the number of CD4+ (T helper) cells, the CD4+:8+ (helper:cytotoxic) ratio, and IL1beta levels. Relaxation training and guided imagery beneficially altered putative anti-cancer host defences during and after multimodality therapy. Such changes...have not been previously documented in a RCT [randomized trial]." [<http://www.ncbi.nlm.nih.gov/pubmed/19008099>]
267. The Department of Pathology, Oregon Health and Science University, Portland found natural killer (NK) cells significantly increased only during active hypnotic-guided imagery intervention. "To determine the effects of hypnotic-guided imagery on immune function and psychological parameters, the following study was undertaken. Psychological profiles, natural killer (NK) cell number and activity were measured at baseline, after the 8-week imagery training program and at the 3-month follow-up. There were significant increases in improvement in depression and increase in absolute number of NK (natural killer) cells, but these were not maintained at the 3-month follow-up." [<http://www.ncbi.nlm.nih.gov/pubmed/12479996>]
268. The Department of Cognitive Neuroscience and Behaviour, Imperial College of Science, Technology and Medicine, London provide evidence of three studies where self-hypnosis was used purposefully to increase immune function, as follows: "Three recent investigations of the author and his colleagues with self-hypnosis training incorporating imagery of the immune system are outlined. In two studies, hypnosis buffered the effects of stress on immune functions in medical students at exam time, and the comparison of self-hypnosis with and without immune imagery confirmed advantages to targeted imagery for both immune function and mood, and importantly, fewer winter viral infections. The implications for health were investigated in a third

study in patients with virulent and chronic herpes simplex virus-2 (HSV-2). Six weeks of [self-hypnosis] training almost halved recurrence, improved mood and reduced levels of clinical depression and anxiety. Immune functions were up-regulated, notably functional natural killer cell activity to HSV-1 (herpes simplex virus). Now that the validation of psychological interventions includes advantages for health, this field of enquiry, which has been characterised by modest, small scale, largely preliminary studies, warrants a greater investment in research." [<http://www.ncbi.nlm.nih.gov/pubmed/12186693>]

269. In a study conducted by the Institute of Psychology, University of Aarhus, Denmark, researchers found using the mind to increase immune function significantly increased natural killer (NK) cell activity. "The present study measured the effects of relaxation and guided imagery on cellular immune function. During a period of 10 days 10 healthy subjects were given one 1-hour relaxation procedure and one combined relaxation and guided imagery procedure, instructing the subjects to imagine their immune system becoming very effective. Even though no major changes in the composition of the major mononuclear leukocyte subsets could be demonstrated a significant increase in natural killer [cell] function was demonstrated." [<http://www.ncbi.nlm.nih.gov/pubmed/2091031>]
270. The Center for Stress Management, Carrboro, North Carolina found visualization significantly increased immune system function. "This psychoneuroimmunological study examined the effects of visualization, or mental imagery, on immune system response, specifically, on depressed white blood cell (WBC) count in 20 medical patients. Subjects were 10 females and 10 males and included medical patients diagnosed with cancer, AIDS, viral infections, and other medical problems associated with depressed WBC count. Results indicated significant increases in WBC (white blood count) count for all patients over a 90-day period, after a predicted initial decrease in WBC count." [<http://www.ncbi.nlm.nih.gov/pubmed/10932336>]
271. In a groundbreaking study, the Minneapolis Children's Medical Center demonstrated that anyone, including children, can modulate the immune system at will using the mind. "In a prospective randomized controlled study, the possibility that children could regulate their own salivary immunoglobulins [antibodies produced by B cells to neutralize bacteria and viruses] was investigated using cyberphysiologic techniques. Fifty-seven children were randomly assigned to one of three groups. Group A subjects learned self-hypnosis with permission to increase immune substances in saliva as they chose; group B subjects learned self-hypnosis with specific suggestions for control of saliva immunoglobulins; group C subjects were given no instructions but received equal attention time. Children in group B demonstrated a significant increase in (immunoglobulin) IgA during the experimental period." [<http://www.ncbi.nlm.nih.gov/pubmed/2642622>]

➤ Evidence of the Link Between Suicidal / Depressive Thoughts and Suppressed Immune System Function

272. The Department of Psychology, University of Pennsylvania, Philadelphia studied HIV positive women with depression and found natural killer (NK) cells increased significantly after the depressive episode resolved. "Depression is a potential risk factor for morbidity and mortality among patients with numerous medical conditions, including HIV disease, and it is also associated with decrements in immune function, such as natural killer (NK) cell activity. HIV-seropositive women were recruited as part of a longitudinal cohort study and underwent comprehensive medical and psychiatric evaluations during a 2-year period. Among the 57 HIV-seropositive women, improvements in the diagnostic status of depression and decreases in scores on the 17-item Hamilton Depression Rating Scale were significantly associated with increases in NK (natural killer) cell activity over time, as measured in lytic units. Eleven women (19.3%) had a major depression diagnosis that resolved over time, and this group also had a significant increase in (NK) cell activity measured in lytic units during this period. This study suggests that depression may impair certain aspects of innate cellular immunity relevant to delaying the progression of HIV disease and that these alterations are reversible with the resolution of a depressive episode." [<http://www.ncbi.nlm.nih.gov/pubmed/16263853>]
273. In a study conducted by the Department of Experimental Medicine, University of Rome, researchers found natural killer (NK) cells were significantly reduced in depressed melancholic patients. "Natural killer cell activity (NKCA) was significantly reduced in a group of depressed patients, melancholic subtype, compared to sex- and age-matched controls." [<http://www.ncbi.nlm.nih.gov/pubmed/2554356>]
274. The Department of Psychiatry, University of Antwerp, Belgium, found depressed melancholic patients had severely weakened immune system function. "Recently, some investigators have established a blunted natural killer cell activity (NKCA) in severely depressed patients. In order to replicate these findings NK cytotoxicity assays--on fresh cell suspensions in human plasma and fetal calf serum--were performed in healthy controls and depressed inpatients. Instead of the commonly used 51Cr-release assay we have used a fluorescent NK

cytotoxicity assay, which allows a greater sensitivity. We observed a significantly blunted NKCA (natural killer cell activity) in melancholic patients as compared with healthy controls and minor depressives, whilst simple major depressives exhibited an intermediate position." [<http://www.ncbi.nlm.nih.gov/pubmed/1542254>]

275. In a study conducted by the UCLA School of Nursing, Los Angeles, researchers found depressed patients recovering from coronary artery bypass grafting (CABG) had significantly lower natural killer (NK) cell activity which resulted in increased microbial infection. "Compared to non-depressed women after CABG (surgery), women with major depression had reduced NKCC (natural killer cell cytotoxicity), more all-cause infections, and more self-reported illnesses. Although NKCC (natural killer cell cytotoxicity) did not mediate the relationship between depression and wound (i.e. incisional) infections after CABG, it did mediate the relationship between depression and non-wound infections, including pneumonias and upper respiratory infections." [<http://www.ncbi.nlm.nih.gov/pubmed/17716947>]
276. In landmark study conducted by the Chonnam National University Hwasun Hospital, Korea, researchers found depressive mood correlated with reduced immune function in breast cancer patients. "We recruited 273 hospitalized patients with breast cancer awaiting surgery. Preoperative plasma samples were obtained for cytokine analysis, including pro-inflammatory (interleukin [IL]-2, IL-12, interferon [IFN]-gamma, and tumor necrosis factor [TNF-alpha]), anti-inflammatory (IL-4, IL-5, IL-10, and IL-13), and immune-modulating (granulocyte / macrophage colony-stimulating factor [GM-CSF]) cytokines. Cytokine levels were significantly inter-correlated. Depressive mood was associated with lower levels of pro-inflammatory (IL-2, IL-12, and TNF-alpha), anti-inflammatory (IL-5, IL-10, and IL-13), and immune-modulating (GM-CSF) cytokines independent of potential covariates such as living area or functional level. The findings suggest that depressive mood is associated with a generally decreased inflammatory reaction or immune function in patients with breast cancer." [<http://www.ncbi.nlm.nih.gov/pubmed/22641927>]
277. In a study of suicidal versus non-suicidal patients, the Shalvata Mental Health Center, Israel, found suicidal patients expressed a unique suicidal over-expression of pro-inflammatory T helper 1 (Th1) cells as follows: "In the following study we have analyzed cytokine secretion of T-cells of suicidal and non-suicidal depressed patients and healthy controls. It was found that T-cells of suicidal depressed patients have Th1 (pro-inflammatory) characteristics, while T-cells of non-suicidal depressed patients have Th2 (anti-inflammatory) characteristics. Th1 environment is associated with most of autoimmune diseases [where the immune system attacks healthy body tissue]. It is thus speculated that Th1 (T helper 1) [cell] activation in suicidal depression may reflect a unique form of autoimmune suicide." [<http://www.ncbi.nlm.nih.gov/pubmed/10232390>]
278. The Department of Psychiatry, Korea University Ansan Hospital found patients with suicidal and depressive tendency had significantly lower immune system function. "In the present study, amounts of IL-6, IL-2, IFN-gamma, IL-4, and TGF-beta1 produced by mitogen-stimulated whole blood were measured in 36 MDD (major depressive disorder) patients who had recently attempted suicide, 33 non-suicidal MDD patients, and 40 normal controls. Suicidal MDD patients had significantly lower IL-2 (interleukin 2) compared with non-suicidal patients and normal controls. Both MDD groups, with or without attempted suicide, had significantly lower IFN-gamma and IL-4 (interleukin 4) production." [<http://www.ncbi.nlm.nih.gov/pubmed/17919797>]
279. In a further study conducted by the Department of Psychiatry, Korea University Ansan Hospital, researchers found patients with major depressive disorder had significantly lower levels of IL-2 (interleukin 2), IL-4 and IFN (interferon)-gamma. "A substantial body of evidence indicates that dysregulation of the immune system is associated with Major Depressive Disorder (MDD). Forty-eight hospitalized MDD patients and 63 normal controls were recruited. At admission, IL-6, TNF-alpha, TGF-beta1 production, and IFN-gamma/IL-4 ratio were significantly higher, whereas IFN (interferon)-gamma, IL-2 (interleukin 2), and IL-4 (interleukin 4) were significantly lower in MDD patients." [<http://www.ncbi.nlm.nih.gov/pubmed/17433516>]
280. In a study conducted by the Ministry of Health of Russia, researchers found a significant decrease in the production of IL-1 (interleukin 1) beta and IL-2 (interleukin 2) in depressive patients. "Interleukin level and mononuclear phagocytes (MPh) activity have been studied in 19 patients with mono- and bipolar depression. The depression was characterized by low MPh activity, a significant fall in IL-1 (interleukin 1) beta production by stimulated monocytes, a trend to reduction of IL-2 (interleukin 2) production by stimulated lymphocytes, significant IL-2 serum concentration increase and significant decrease of soluble IL-2 receptor (sIL-2R) concentration in the serum. MPh (the main IL-2 producers) activity reduction results in the monocyte IL-1 beta production decrease followed by changes in interleukin (in particular, IL-2) production by lymphocytes and other changes in interleukin system." [<http://www.ncbi.nlm.nih.gov/pubmed/11586704>]

281. In a groundbreaking study conducted by the Institute of Mental Health, Tomsk Scientific Center, Siberian Division, Russian Academy of Medical Sciences, researchers found depressive patients had significantly higher rates of programmed cell death / cell suicide [known as apoptosis] in immune system [T cell, B cell and natural killer (NK) cell] lymphocytes, providing evidence depressive mood suppresses immune function. "A comprehensive evaluation of biological indices has been carried out in 26 patients with depressive disorders and in 20 age- and sex-matched controls. Indices of programmed cell death (apoptosis) in subpopulations of blood [immune system cell] lymphocytes and concentration of cortisone in blood serum were determined. Significantly enhanced apoptosis (cell suicide) was observed in the [immune cell] lymphocytes of depressive patients as shown by increased percentage of [immune] lymphocytes expressing FAS-receptor and cells with morphological changes characteristic of apoptosis (nuclear condensation, vacuolation. Clinical symptoms of depression were concomitant with alterations of cellular link of immunity expressing in the decrease of the total T-lymphocytes (CD3+) number, T-helpers (CD4+) and natural killers (CD16+) as compared to healthy persons. The level of blood serum cortisone (cortisol) was increased in patients with depression. High cortisone values correlated with suppression of cellular CD4+ population and an increase of FAS-receptors expression in patients with depression." [<http://www.ncbi.nlm.nih.gov/pubmed/16768226>]
282. A study conducted by the Shalvata Mental Health Center, Israel found depressed patients had significantly higher rates of programmed cell death / cell suicide [known as apoptosis] in immune system [T cell, B cell, natural killer (NK) cell] peripheral blood lymphocytes (PBL's). "Apoptosis is a programmed cell death that can be observed in normal cells. Major depression poses a combination of a depressed and destructive auto-immune reaction. We measured apoptosis in the [immune system cell] PBLs (peripheral blood lymphocytes) of seven patients with major depression and in age and sex-matched controls. We observed significantly increased apoptosis (cell suicide) in the PBLs (peripheral blood lymphocytes) of depressive patients. Our results can explain findings obtained by others that showed reduced NK (natural killer) activity and lower mitogen (cell division) stimulation in depressed patients. Some of these observations can be attributed to the increased apoptosis in these cells. This pattern may suggest a "suicidal" tendency of the immune system in depressed patients and could lead to a vulnerability of the immune system, with decreased ability to resist infections, tumors, or autoimmune diseases." [<http://www.jimmunol.org/content/163/1/533.full.pdf>]
283. The Department of Psychiatry, San Diego Veterans' Affairs Medical Center found acute depression lowers natural killer (NK) cell immune system function. "Cross-sectional studies have demonstrated that natural killer (NK) cell activity is reduced in depression. To extend these observations and examine further the association between severity of depressive symptoms and values of NK activity, this study used a longitudinal case-control design and assessed NK cytotoxicity at intake and at follow-up 6 months after discharge from the hospital in depressed patients and control subjects. From acute hospitalization to follow-up, depression scores significantly decreased following treatment in the depressed patients but did not change in the control subjects. NK activity significantly increased from intake to follow-up in the depressives while lytic activity did not change in the controls. At intake NK activity was significantly reduced in the depressed patients as compared to values in the controls, while at follow-up (NK) cytotoxicity was similar between the two groups. These longitudinal data suggest a reduction of NK (natural killer cell) cytotoxicity is temporally associated with the state of acute depression." [<http://www.ncbi.nlm.nih.gov/pubmed/1488477>]

➤ Evidence of the Link Between Suppressed Immune System Function & Increased Viral-Bacterial-Fungal Infection

284. In a study conducted by the Department of Microbiology, Stritch School of Medicine, Loyola University of Chicago, researchers found IL-2 (interleukin 2) inhibited the growth of the common human fungus *Candida albicans*. "Previous reports have demonstrated natural killer cells (NK) to exert growth inhibitory effects against certain fungi, but not against *Candida albicans*. In this investigation, interleukin-2 (IL-2)-induced lymph node cells with phenotypic and functional characteristics of NK were shown to inhibit the growth of *C. albicans*." [<http://www.ncbi.nlm.nih.gov/pubmed/2188739>] "We have shown previously that IL-2-activated splenocytes can inhibit the growth of *Candida albicans* hyphae in vitro. Herein we demonstrate that plastic nonadherent [T cell] lymphocytes that are CD8+ mediate the antifungal activity. Enrichment for CD8+ cells markedly enhanced the antifungal activity of the IL-2 (interleukin 2)-activated lymphocyte population for *C. albicans* and the cytotoxic activity of the lymphocytes for an NK-resistant cell line. Depletion of CD8+ cells reduced the lymphocyte population's antifungal activity and cytotoxic activity for the NK-resistant cell line. These data show that IL-2-activated CD8+ T [cell] lymphocytes exert the greatest amount of antifungal effect against the hyphal [fungal] form of *C. Albicans*." [<http://www.ncbi.nlm.nih.gov/pubmed/7730631>]
285. Oral candidiasis or thrush is a common fungal infection found in those with immune deficiency, particularly those with HIV/AIDS. In a study conducted by St. Michael's Hospital, University of Toronto, researchers found

thrush developed only in HIV+ individuals whose immune system was severely compromised. "One hundred and twenty-seven patients with HIV infection were divided into 3 groups according to the CD4+ lymphocyte (T cell) count, and 37 healthy volunteers served as controls. Persistent carriage of yeast and development of clinical thrush were associated with lower CD4+ counts. Clinical thrush developed only in patients with persistent asymptomatic carriage of [fungus type] *C. albicans* and CD4+ counts [severely compromised of] less than 500/microL." [<http://www.ncbi.nlm.nih.gov/pubmed/7730631>]

286. In a review of patients conducted by the Ministry of Medical and Microbiological Industry USSR, researchers found immune-depressed cancer patients had a higher degree of fungal infection. "Lately the frequency of fungal infections in oncological patients considerably increased. The cause is a decreased immune status and in particular decreased immunity against fungal infections in oncological patients because of the oncological disease and aggressive treatment. In the patients treated with immunodepressants the frequency of [fungal infection] *Candida* vegetating on the skin and in open cavities was higher. Fungi were isolated from the pathological materials of 8.9 per cent of the patients in 1981, 12 per cent in 1990, 17 per cent in 1991 and 24 per cent in 1992." [<http://www.ncbi.nlm.nih.gov/pubmed/7826175>]
287. In a study conducted by the Division of Haematology, Third Department of Internal Medicine, Nippon Medical School, Tokyo, researchers found a direct link between lower natural killer (NK) cell activity and increased microbial [fungal] infection and subsequent incidence of death in nursing home residents. "Congenital patients who lack natural killer (NK) cell activity experience repeated polymicrobial (viral-bacterial-yeast-like-fungal) infections. NK cell activity varies significantly among normal people, but it is unknown whether this variation influences their ability to fight infections. This study examined this concern. NK cell activity and other variables, i.e. age, sex, performance status (PS), serum albumin value, lymphocyte and neutrophil counts, various lymphocyte subsets, etc. were determined for 108 immunologically normal elderly subjects who were in nursing homes due to an impaired PS (performance status). We analysed for correlations between these variables and the follow-up results of the subjects. Forty-eight subjects developed infection(s) during the first year of follow-up. A low NK cell activity was associated with the development of infection. The relative risk for the development of infection increased in accordance with the decrease in the NK cell activity. Eleven subjects died of infection during the study period. A low NK cell activity was associated with short survival due to infection. Our data indicate that low NK cell activity is associated with development of [viral-bacterial-yeast-like-fungal] infections and death due to infection in immunologically normal elderly subjects with an impaired PS." [<http://www.ncbi.nlm.nih.gov/pubmed/11472399>]
288. In a study conducted by the Section of Pulmonary and Critical Care Medicine, School of Medicine, Louisiana State University Health Sciences Center, researchers found natural killer (NK) cells and (CD4) T cells prevent *Pneumocystis* [fungal] pneumonia infection. "Using our murine model of *Pneumocystis* pneumonia, we found that loss of NK cells during immunosuppression results in substantial *Pneumocystis* lung burden. During early infection of CD4(+) T cell-depleted mice, there were significantly fewer NK cells in the lung tissue compared with CD4(+) T cell-intact animals, and the NK cells present demonstrated decreased upregulation of the [NK cell protein] activation marker NKp46 and production of the effector cytokine, IFN- $\gamma$  (interferon gamma). Furthermore, coinubation studies revealed a significant increase in fungal killing when NK cells were combined with CD4(+) T cells compared with either cell alone, which was coincident with a significant increase in [fungal killing] perforin production by NK cells. Finally, however, we found through adoptive transfer that memory CD4(+) T cells are required for significant NK cell upregulation of the activation marker NK group 2D and production of IFN- $\gamma$ , granzyme B, and perforin during *Pneumocystis* infection. To the best of our knowledge, this study is the first to demonstrate a role for NK cells in immunity to *Pneumocystis* pneumonia, as well as to establish a functional relationship between CD4(+) T cells and NK cells in the host response to an opportunistic fungal pathogen." [<http://www.ncbi.nlm.nih.gov/pubmed/23203926>]
289. The Department of Medical Microbiology and Hygiene, Technical University Dresden, Germany found mice deficient in IL-2 (interleukin 2) and raised in a pathogen-free environment, subsequently develop colitis from bacteria that has pleomorphised (grown) from within their own bodies. "Raised under specific-pathogen-free conditions, interleukin-2-deficient mice develop an inflammatory bowel disease resembling ulcerative colitis in humans. Fluorescence in situ hybridization identified up to 10% of the mucosa-associated flora in (IL-2) interleukin-2-deficient mice as [bacterium] *Escherichia coli*, whereas no *E. coli* was detected in the mucosa from healthy wild-type mice. The abundance of *E. coli* in the colonic mucosa of interleukin-2-deficient mice strongly suggests a participation in the pathogenesis (disease progression) of [bacterium produced] colitis in the interleukin-2-deficient mouse model." [<http://www.ncbi.nlm.nih.gov/pubmed/15039318>]

## About the Author

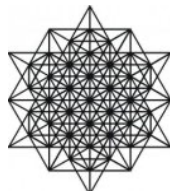


Glen Russell: I have served as a spiritual channel for God since 2002. I do not prophesize nor predict the future, but serve as a receiving point, instrument and scribe for the download of new information and concepts from God. This has been a gradual process and I have been tested rigorously by God to ensure the information I am receiving and subsequently writing down is of the highest accuracy. Many of the pieces of the cancer puzzle which God has chosen to bring forward in this document are new concepts. Designed for medical practitioners, researchers and lay folk, this is a working document that does not assert itself as the final answer or solution to cancer, but brings together a cohesive understanding of the causal link between psycho-emotional stress and cancer. As a working document its role is to challenge pre-conceived misunderstandings and stereotypes within the field of oncology and to evoke continual discussion and open-minded evaluation. Due to the sensitive nature of this field and its importance, God has readied his scribe for the purpose and since 2002 I have trained as a hypnotherapist, counsellor, EFT practitioner and served as a seat or open-channel for God's words to flow through in the healing of individuals who are seeking to heal psycho-emotional dis-ease which often manifests as physical dis-ease. In 2006 I undertook further training as a hypnosis-for-cancer specialist through the Omni Hypnosis Training Centre, Florida, and undertook a specialized training program with Stephen Parkhill, author of *Answer Cancer*, using hypnosis to heal the psycho-emotional cause of cancer. Since then I have worked with hundreds of patients seeking to heal the root psycho-emotional cause of their cancer. My decision to specialize in the field of psycho-oncology has come about as a pre-ordained decision by my soul to serve God in this capacity, and was awakened at the human level by my own personal experience with cancer. In 1992 my mother was diagnosed with breast cancer and passed away in 1997. As her caregiver and son I struggled to find a cure for the illness that was threatening to take my mother's life, but with no internet availability at the time and my limited knowledge, our final route was intravenous vitamin c therapy; which having stopped due to limited funds, brought about her passing swiftly due to a sudden drop in vitamin c levels. This experience affected me deeply and ignited within me seven years later a calling to help others who are facing the cancer storm. I would like to share also the story of my elderly grandmother. In 1980 she went in for a bowel operation where the doctors discovered she had bowel cancer and removed most of it, however because they could not remove all of it they told my grandfather she had at most a year to live. To protect my grandmother the family made a decision not to tell her she had cancer, which of course sounds [and sounded to me at the time when I was 9 years old] --- incredulous, but understandable. What was even more incredulous, she lived for another ten years, passing away from natural causes. This echoed within my consciousness from an early age that cancer is indeed a disease of the mind.

## Acknowledgements



I would like to take this opportunity to thank my mother and grandmother for serving as inspirations in helping to awaken me to my life's soul-purpose in this field of psycho-oncology. I would also like to thank my spiritual partner Arthur King of Puna Wai Ora Healing Centre for his ongoing support who is committed to serving God. Finally, I thank God and God's Angels of Light and the Spiritual Hierarchy of God's Infinite Being who guide us unwaveringly into a higher state of awareness and enlightenment by sharing God's Infinite Wisdom, Knowledge and Truth.



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