Hyperhidrosis is caused by trace amounts of heavy metals (arsenic, lead, mercury, etc.) biomethylatating into a more toxic/volatile form than the parent compound, resulting in toxic encephalopathy of the pituitary gland, ensuing dephosphorylation of CREB in times of stress.

P. S. O'Callaghan, independent researcher, pocallaghan65@yahoo.com, February 25, 2013

A perspective from someone who has suffered from hyperhidrosis and insomnia for over 30 years.

Abstract

Hyperhidrosis should be classified in the Psychological DSM IV manual as a "stress disorder dysfunction" caused by toxic encephalopathy of the pituitary gland. Ingesting of food or contaminants containing heavy metals is processed by the liver differently, into a more toxic reactive form than the parent compound, in hyperhidrosis patients compared to normal subjects. This toxic substance enters the blood stream and makes its way to the pituitary gland, resulting in an exasperation of the HPA axis and desensitization of the pituitary gland in times of stress. The hyperhidrosis patient's interpretation of the stressful event and toxic encephalopathy of the pituitary gland accelerates dephosphorylation of cAMP response element binding (CREB) protein. This process causes oxidative stress and cellular antioxidants to be out of sequence, such as high levels of superoxide dismutase (SOD), malondialdehyde (MDA) and low levels of catalase (CAT), glutathione peroxidase (GSH-px). The cellular antioxidants are out of sequence because they trying to break down excessive levels of hydrogen peroxide (H2O2). This excess production of H2O2 is trying to activate CREB (I call it a feedback loop). The human body counteracts this surplus production of H2O2 by breaking it down into excess amounts of water. This additional amount of water passes through areas of the body that have the greatest concentration of sweat glands, which results in hyperhidrosis. Other factors that could also be involved in this metabolic disturbance associated with hyperhidrosis are, a mutation in arsenic methyltransferase (AS3MT), tumor necrosis factor alpha (TNF-alpha), Nitric Oxide (NO), interleukin 6 (IL-6), IL-1, IL-10 and tumor interferon gamma (IFN-gamma), Ghrelin, Cholecystokinin (CCK), H2O2 neutralizing Hydrogen Sulfide (H2S), Bcl-2-associated X protein (Bax), mutation in the hepatocellar transport protein ABCB4 (MDR3) or bile acid becoming toxic to hyperhidrosis patient. Conclusion: Hyperhidrosis is caused by toxic encephalopathy of the pituitary gland (irritation of the pituitary gland) caused by a more toxic/volatile form of trace amounts of heavy metals, which results in excess production of H2O2, and dephosphorlation of CREB in times of stress.

Methods

I performed a www.pubmed.org and internet search's using key words, "arsenic, arsenic and stress, arsenic and pituitary gland, CREB, hyperhidrosis, CREB and stress, hydrogen peroxide, heavy metals and etc.," I searched many articles, and abstracts of articles, to form a basis for this theory.

Introduction

Hyperhidrosis causes great psychological distress in the patient's life and little attention has been spent by the medical community in the underlining cause of this disorder. I have spent over 20 years trying to piece together this complex puzzle. I have to remind everyone reading this paper that I am not a doctor or

a biophysicist and have no medical background training. I wrote this paper hoping to persuade a doctor or university to do further research in what I am proposing. This is my theory on paper and I am hoping a smart, above average doctor can find the root cause of my condition. Since the material I encountered was overwhelming, I regurgitated most of the material stated in my paper.

My first paper is the theory and cause of hyperhidrosis, entitled, "Is the transcription factor protein CREB the cause of hyperhidrosis," I believed for many years there was a genetic mutation in the CREB protein in times of stress which was the root cause of hyperhidrosis. Further research, on my part, has revealed heavy metal toxicity, especially arsenic, is being processed in the liver into a more toxic form, resulting in hyperhidrosis. I believe these more dangerous toxic substances are simply an **irritation of the pituitary gland** in times when the hyperhidrosis patient interprets a stressful event. That is why test results to indicate a dysfunction of the pituitary gland, produce normal results. Somehow hyperhidrosis patients are processing these toxic forms of heavy metals, in an unknown way, so these toxins do not overwhelm the body, especially the pituitary gland.

The majority of this paper concentrates on arsenic, but I believe the word arsenic can be substituted with any other heavy metals, such as lead, mercury, etc.

At first thought you might think why would arsenic cause hyperhidrosis. From the outside looking in it makes no sense. I for one do not have any of the symptoms of arsenic poisoning, and people suffer from low exposure to arsenic do not have hyperhidrosis symptoms. So how is arsenic the trigger behind hyperhidrosis? Throughout my paper I will try to prove indirectly that the more toxic form of heavy metals is the cause of hyperhidrosis.

In humans inorganic arsenic is metabolized via two main types of reaction, (1) conversion of the pentavalent form of arsenic-arsenate-to the trivalent form-arsenite, and (2) methylation. After methylation arsenic can be rapidly eliminated from the body with the urine. There can be large differences between individuals in their capacity for methylation that is most likely due to differences in enzyme capacity in the body.

Arsenic is considered a heavy metal and shares many toxic characteristics with other heavy metals (example, lead, mercury, aluminum, chromium, cobolt, manganese, nickel, selenium, zinc, tin and thallium). Arsenic may be found in food (fruits and vegetables) and water. Inorganic forms of arsenic are more toxic than the organic forms. The elemental form is not toxic but the oxides are extremely toxic. The trivalent forms are more toxic and react with thiol groups, while the prevalent forms are less toxic but uncouple oxidative phosphorylation. The elemental very few organ systems escape the toxic effects of arsenic. Trivalent inorganic arsenic inhibits private dehdrogenase by binding to the sulfhydrl groups of dihydrolipoamide. Consequently, conversion of private to acetyl coenzyme A is decreased, citric acid activity is decreased, and production of cellular ATP is decreased. Trivalent arsenic inhibits numerous other cellular enzymes through sulfhydrly group binding. Trivalent arsenic inhibits cellular glucose uptake, gluconeognesis, fatty acid oxidation, and further production of acetyl coenzyme A, it also blocks the production of glutathione, which prevents cellular oxidative damage. Arsenic produces oxidative stress alternating monocyte super oxide anion production and inhibiting nitric oxide production. Frequently, patients exposed to arsenic have a garlic smell to their breath and tissue fluids (I do not have garlic smell to my breath, but have intense body odor after LD). For acute arsenic ingestions, lavage is recommended. Activated charcoal does not adsorb arsenic appreciably. Whole bowl irrigation with polyethylene glycol may be effective to prevent GI tract absorption of arsenic, according to Dr. Steven Marcus, of University of Medicine and Dentistry of New Jersey.

Arsenic binds to a range of sulphydryl containing proteins. These include enzymes involved in oxidative metabolism (leading lactic acidosis, shock, hemoglobin synthesis (leading to a sidercoytic anemia andmethionine synthetase (leading to homocysteinaemia). Arsenic is distributed into red blood cells rapidly and binds to hemoglobin. Distribution to other tissues occurs over 24 hours, except for arsine gas, which remains largely confined to the red cells. The majority or arsenic measured in blood is contained within red cells. Thus in people with anemia, the blood arsenic concentration may underestimate the total body arsenic. Arsenic is excreted renally. Following an acute exposure, there is an initially relatively rapid fall in concentrations (half-life 24 hours), with a terminal elimination half-life in the order of 10 days. With chronic exposure, there is likely to be substantial amounts in tissue stores, that is slowly eliminated and not available for chelation. Acute toxicity from trivalent arsenic (arsenite) compounds occurs a lower does than from prevalent arsenic (arsenate) compounds. The usefulness of chelation therapy in long term chronic exposure is probably very limited according to Open Source Clinical Toxicology Curriculum, found on internet.

For soluble trivalent arsenic compounds, approximately 95% of the ingested dose is absorbed from the GI tract. After absorption through GI tract, arsenic is widely disturbed by the blood throughout the body. Most tissues rapidly clear arsenic, except for skin, hair and nails, even after 2 to 4 weeks. Reduction of arsenate (As V) to arsenite (As III) is needed before methylation can occur, this reaction requires glutathione. A portion of arsenite is methylated in the liver by enzymatic transfer of methyl group from S-adenosylmethionine (SAM) to methyl arsonate (MMA V) and dimethyl arsenate (DMA V). The resulting metabolites are more readily excreted. Methylation has long been considered the main route of arsenic detoxification, but more recently there has been a growing body of literature supporting other detoxification mechanisms. For example, a number of animal species lack arsenic methylating and excrete inorganic arsenic. The implication is that there may be other more important arsenic detoxification mechanism in mammals such as antioxidant defenses, resistance to apoptosis. There have also been studies of arsenic metabolism suggesting that methylation of inorganic arsenic may be an oxidation, rather than a detoxification pathway and that trivalent methylated arsenic metabolites, particularly monomethylarsonous acid (MMA III) and dimethylarsinous acid (DMA III) are usually capable of interacting with cellular targets such as proteins and DNA. Methylation efficiency in humans appears to be genetically linked. When the methylating capacity of the liver is exceeded, exposure to excess levels of inorganic arsenic results in increased retention arsenic in soft tissues. Arsenic is primarily excreted through the kidneys, and less important elimination routes are feces, incorporating into hair/nails, skin desquamation and sweating (Sweat in hot, humid environment can eliminate 2 ug of arsenic per hour), according to the agency for toxic substances and disease registry, October 1, 2009.

The toxic effects caused by acute exposure to arsenic troxide are due its ability to bind to cellular proteins containing sulfhydryl groups. This inhibits the production of energy needed to maintain tissue function, and results in a decrease in glutathione, which is necessary for the metabolic detoxification of arsenic. The primary target organs are the gastrointestinal tract, heart, brain and kidneys. Eventually the skin, bone marrow and peripheral nervous system are also affected according to Medical Management Guidelines.

Arsenic interferes with cellular longevity by allotter inhibition of an essential metabolic enzyme private dehydrogenase (PDH) complex, which catalyzes the oxidation of private to acetyl-CoA. With enzyme inhibited, the energy system of the cell is disrupted resulting in a cellular apoptosis episode. Biochemically, arsenic prevents use of thiamine resulting in resembling thiamine deficiency. Poisoning with arsenic can raise lactate levels and lead to lactic acidosis. Low potassium levels in the cells increase the risk of experiencing life threatening heart rhythm problem from arsenic trioxide. **Arsenic in cells clearly stimulates the production of Hydrogen Peroxide (H2O2).** When H2O2 reacts with certain metals such as iron and manganese it produces a highly reactive hydroxyl radical. H2O2 production is also increased, which might form reactive oxygen species and oxidative stress.

Background

My hyperhidrosis and insomnia began at puberty, between the ages of 12 and 13. However, I believe I have been afflicted with an **overactive fear/hyper-arousal mechanism** my entire life, which began early on in my life. For example, the first day of kindergarten I ran out of the school building terrified and crying. To this day, I cannot understand why I was so afraid. However, once I settled into my surroundings, I looked and acted like any normal boy. I also slept with the light on as a child, because I was afraid of the dark, thinking I would be attacked by a monster. Also, I was terrified to have my hair cut by the barber. These examples I listed above would be described by a psychologist as social anxiety. It is true anxiety plays a role in hyperhidrosis, but anxiety plays a role to some extent in every ones' lives. I believe sufferers of hyperhidrosis are hyper-aroused and not anxiety ridden. I believe there is a clear distinction between the two. It is similar to the chicken and egg theory, does the sweating causes anxiety or vice versa????

When I reached the age of puberty, my sweating was mostly concentrated under my arms (axillary) and feet (plantar). My axillary sweating was so extreme that I was forced to wear diapers to prevent my shirts from being covered in perspiration. After a certain amount of time, depending on the stressful event, the

diapers would fail in their job and the sweating would make its way through my shirt. At the age of 17, I tried tap water Iontopheresis for my axillary hyperhidrosis. It worked successfully for the first few days, but soon afterwards I quickly developed compensatory sweating around my face. To this day, I still suffer from the compensatory side effects of this treatment. Once the sweating starts around my face I become very self-conscious, afraid someone will notice and make a comment. This situation usually triggers a panic attack, thus resulting in my entire body to be covered in perspiration. For many years my hyperhidrosis has progressed to encompass my entire body, even the palms of my hands. I believe this has occurred mainly because I am trying to lead a normal life and take on more responsibility. Since hyperhidrosis is a stress disorder, it makes sense that an increase in stress and responsibility would cause an increase in sweating. To a trained psychiatrist I would be labeled as someone suffering from anxiety or low self-esteem, however that could not be further from the truth. There might be some overlapping symptoms of my disorder with anxiety, but it is not the cause. Something more, in my metabolism, is responsible for my condition. I would simply describe myself as in a hyper-aroused state my entire life; **only under stressful** situations or my interpretation of stressful events (similar to being on a mild form of speed or having a never ending cup of coffee throughout the day). It feels like my adrenal glands are set in the on position and cannot be regulated or controlled (according to lab results my adrenal glands are functioning normally).

There is a genetic aspect to my disorder, which is very common with people who suffer from hyperhidrosis. The majority of people afflicted with hyperhidrosis have a least one family member that suffers from its effects. In my case, my maternal grandfather suffered from hyperhidrosis his entire life. At this time, I am also listing other medical family background information that could be relevant in figuring out the puzzle of hyperhidrosis and insomnia. First, my mother suffers from high cholesterol (good and bad), insomnia, psoriasis (as a teenager her psoriasis developed soon after a stressful event occurred in her life), psoriasis disappeared briefly while she was pregnant with me (she took Depo-Provera while pregnant with me), she had three miscarriages (mice born with an inactive CREB died immediately after birth), **hypersensitivity to sulfur** drugs/water (develops rash), **allergic to penicillin**, Hypoglycemia and has a history of **gallbladder discomfort/trouble**. Also, the majority of family members, on my mother side of the family, have had a history of gallbladder trouble and some of them had their gallbladders removed (in 2011 **I** started developed discomfort in my gallbladder area, which usually occurs at night, while trying to sleep on my right side. This occurred if I ate **garlic** for dinner and was on antibotics at the time). Also, there is also a history of Dementia on my mother's side of the family. Furthermore, my maternal grandmother developed rheumatoid arthritis at the age of 30 (her rheumatoid arthritis developed soon after a stressful event occurred in her life). On my father's side of the family there is history of alcoholism (grandfather and uncles suffered the effects of alcoholism) and diabetes (the diabetes has appeared in my father's generation only). My father smoked almost his entire life. He suffered briefly from Globus Hystericus (psychological) for a brief period of time. My father had a low tolerance for alcohol, and sometimes the alcohol made him physically sick, even if he ingested a few beers (I too, have noticed low tolerance for alcohol). However, both sides of my family are basically healthy and have a history of living into their 80's and 90's (diabetes that appeared in my father's generation, relatives died early, in 50's and 60's).

In 2005, I contracted Lyme Disease (LD) and was treated with the standard one month treatment of oral antibiotics. The "C minus" doctor would not extend the treatment because she felt "the standard one month's treatment procedure" was adequate and conformed to current medical treatment standards, despite the fact I clearly told her I was suffering from the continuing effects of LD. This inadequate treatment procedure resulted in a five year nightmare for my wife and me. For three years, after contracting LD in 2005, I went from one doctor to another trying to find out what was causing me to feel so sick (eleven doctors in total over that three year period). Over this period of time the LD slowly festered in my body and I became sicker by the month. Since I received the standard one month's treatment of antibiotics, none of the doctors I saw believed I was ill. The doctors came up with this theory, because all basic blood work was normal, including the 10 Western Blot LD test. The problem with the standard, lab production line, 10 Western Blot LD test is that it is false positive 50% of the time. At work I twice briefly lost conscious and the doctors still did not believe I was ill or could not figure out what was wrong with me. In 2008 I fell apart completely, and was not able to function physically or mentally. Fortunately I found a doctor who specializes in LD and diagnosed me immediately with the continuing effects of LD. At that time, Dr. Eiras of Jackson, NJ (who also suffers from LD) ordered extensive lab work which reveled LD had caused: IGeneX IgM 10 Western Blot LD test showed positive bands at 23-25 and 41, slight elevation

in red blood cell count, impairment to my immune system (my immune system almost collapsed, proven with CD57 striker panel blood test, Labcorp, a healthy immune system should test around 200, I had a test score of **22**.), low levels of vitamin D and **significant elevations of norepinephrine** (elevation where so high, two independents doctors thought there might be a possibility I had a tumor on my adrenal glands, epinephrine levels where normal ??????), **catecholamine, pneumonia, herpes simplex I/II and Epstein Barr virus**. During the nuclear treadmill stress test I experienced intense pressure on my chest and almost passed out, and could not complete the test. Prior to LD I had no difficulty running a mile.

In 2007 I developed a herniated disk in my neck (C5-6), and briefly lost use of my left arm (I believe now this was caused by LD evading another weak part of my body). I injured this area of my neck during a high school football game in 1983. For a period in 2007, for six months, I was working almost 80 hours a week of physical labor. During this time I struggled every day to get through the day, I was physically weak and tired {at this time I did not know I was suffering the continuous effects of LD}. I lost a lot of weight. For a brief period of time, at the end of the six months, I was normal again, sleeping and sweating the same prior to LD. A few days after I stopped working, I unexpectedly lost use of my left arm while walking in the department store and experienced chest discomfort and dizziness. I believe now the LD invaded the C5-6 disk in my neck from my brain stem. It is very interesting, since my LD has stabilized, the florescence lights in a department store always retrigger my LD after about 15 minutes. I become physically sick and develop cognitive dysfunction, because of the florescence lights. Because I lost use of my left arm and was under extreme pain from the herniated disk, I was given an oral steroids and injections which I caused my LD to be reactivated.

At the height of the LD, in 11/09, my Alanine Transaminase (ALT) and Angiotensin Converting Enzyme (ACE) where significantly above normal limits.

Also, my testosterone levels had fallen well below normal range and was comparable to a 70 year old man (stated by the Endocrinologist and Dr. Eiras). Published in the Science Daily, Nov. 10, 2004, the Mayo Clinic in Rochester Minnesota discovered decreasing testosterone boots immunity because testosterone helps control T-lymphocytes, the attack cells of the immune system. They found testosterone seems to impede immunity according to Dr. Kwon. He also states that when testosterone is withdrawn, you get an increased host immune response indicated by the rising number of immune cells that are available to participate. The presence of testosterone slows or weakens the response of T-lymphocytes. The research team also found out that without testosterone, the T-lymphocytes "turn-on" more quickly. I believe my body was purposely suppressing testosterone levels to boost my immune system while it was fighting LD. When my LD slowly stabilized, and I started to slowly feel better, (mainly due to the drug Acotos) my testosterone levels have risen slowly to normal levels (**my testosterone is always tested in the normal range, but on the low side of normal**). This one occurrence proved to me that my body is functioning normally and is adapting to a defect in my gene sequence that is occurring in my body my entire life. Somehow, my body is also adapting to the more toxic form of heavy metals and processing these toxins in an undiscovered way, resulting in hyperhidrosis.

The LD also caused my hyperhidrosis and insomnia to reach a new level of intensity that I have never experienced before. For example, the sleep deprivation I experienced was so extreme that I would go days without any sleep. At one point I thought someone was injecting adrenaline into my blood stream every day. On some days I could actually feel the adrenaline surging through my body. When I was finally able to fall asleep, it would be for only 1 hour and would be unable to nap at all during the day. During that short period of time of sleep, only my head and neck became drenched in perspiration (this occurred every day for almost one and half years). Prior to LD I never perspired at night unless I had a flu or fever. This malfunction in the sleeping cycle, caused by LD, produced violent nightmares almost every time I closed my eyes or **REM Sleep Behavior Disorder or Night Terrors**, where I shouted and punched a perceived aggressor. Suffering through years of extreme sleep deprivation, caused by LD, lead to the development of severe depression and suicidal thoughts. On a few occasions I reached the breaking point, and prayed to GOD for Him to kill me (strongly considered suicide at this time and wanted to end my life. Now I know why people use sleep deprivation as a torture technique. Looking back now, I realize I was slowly losing my mind during this very difficult time in my life). During my struggle with sleep, associated with LD, I always felt warm, increase in body temperature. Prior to LD I averaged about 4 hours of sleep per night (it never was a good sleep, I would describe my sleep as a transit like state) and had the ability to nap during the day and on weekends.

In April of 2011 I tried Alpha-Stim. Dr. Eiras thought it might help my insomnia, but it did not. However, it did stop my sweating at night, caused by the LD, and improved my cognitive function. Prior

to using the Alpha-Stim, I had a difficult time functioning at work (construction), but somehow the Alpha-Stim improved my cognitive function caused by the LD????

Other symptoms I experienced with LD: extreme fatigue, experience amphetamine like response most of the day, flu like symptoms, knife stabbing chest pain/pressure on chest (left leg and arm became numb/tight), shooting pain down left leg, brain fog, cognitive impairment (on some days I could not spell, write, form basic sentence structure, read and perform simply arithmetic), Alzheimer's symptoms (briefly became lost in my back yard, did not know who I was or where I was), depression, increase in the intensity of panic attacks, difficulty finding the right words in speech, could not reverse words/subtracting from 100 by 7's, decrease in sexual interest, lack of coordination (felt drunk), difficulty with fine motor tasks, difficulty driving (drove on wrong side of road and did not even know it until a car was coming straight at me; hard time making left turns. I became lost driving in familiar places), sometimes my left hand was curled up at my side, sometimes left arm jerks for no apparent reason when I try to grab an object, left arm/leg jerk/twitches, whole spontaneous body jerks (these jerks still continue to this day), intense ringing/buzzing noise in ears, increase in body odor under my underarms (even after I came right out of the shower), load noises went through me like a knife, constant sore throat, experienced weird colds, I felt hot all the time (skin felt hot), extreme fluctuations in body temperature, out of control temper (Lyme rage, this out of control temper almost cost me my marriage), sharp pain in gallbladder area, Guttate Psoriasis (small white dots over my chest and back). Almost a dozen times, during this 5 year nightmare, my wife was ready to take me to the emergency room because I felt like I was going to die. A few times I dialed 911 into my cell phone and I was seconds away from pushing the send button, because felt like I was going to die (experienced intense knife stabbing chest pain, discomfort and pressure).

The reason I described my battle with LD in great detail because the doctors discovered a lesion, or white matter on my brain stem. Historically, LD always attacks the weakest part of the human body and mind (it simply highlights any weakness in your body). LD is known as the "great imitator" because it mimics so many disorders from gout, arthritis, MS, ALS, neuropsychiatry disorders and many other illness. The MRI, with and without contrast, report stated and read, "nonspecific abnormal signal in the posterior midline of the pons. This is near the floor of the 4th ventricle and correlation with the patient's clinical examination is recommended." Why did the LD invade this particular part of my brain????? I can only theorize that this part of the brain might be responsible for hyperhidrosis or insomnia. The MRI also stated, "post contrast imaging demonstrates the presence of a small developmental venous anomaly in the left frontal region." An hour after the MRI I experienced extreme fatigue. It felt like every ounce of my energy was sucked out of me, which forced me to lay on the couch for over 4 hours, because I was physically unable to move. I also experienced extreme cognitive impairment and chest pain. Maybe the die injected into the blood stream interacted with the LD and caused a Herxheimer Reaction????? I do not know.

As I stated before, when I developed LD my hyperhidrosis and insomnia reached a new level of intensity. For example, while I was watering the plants outside of my home I became drenched in perspiration within half an hour. During this time rivers of sweat where pouring from my head and body. I describe the level of sweating as biblical. On this particular day it wasn't hot out and I wasn't working very hard. These examples, listed above, of the symptoms of LD gives the reader some indication of the powerful effect this disease has on me, or it might help point to a clue about the cause of hyperhidrosis and insomnia. **Prior to the tick bite in 2005, I never experienced any of the symptoms listed in the previous paragraphs. To sum things up; LD has been a living nightmare for me.**

For over a two years, since October of 2008, I have been on oral antibiotics, IM antibiotics, anti-viral, anti-malaria drugs and numerous vitamins for my LD. These drugs and vitamins had a very limited effect in reducing the symptoms of LD. In fact I was getting worse, based on the blood test CD57 striker panel (Labcorp), which tests the strength of your immune system. **I also experienced sharp pain in the gallbladder area** during my treatment with oral antibiotics and had severe bouts of diarrhea.

In January of 2010 I started Actos, on my own, and showed improvement in LD symptoms, but relapsed occurred in June when stopped using Actos (look in treatment section for greater detail how Actos help improve immune system????????). In July of 2010 I started with IV Zithromax (total of 24 treatments) and Actos, which slowly starting to show some positive results. For the first 5 treatments of IV Zithromax I experienced an intoxicating feeling, similar to having 4 beers. I lost conscious twice while on IV Zithromax.

I believe oral antibiotics had a limited effect on my LD, because of how medicines are processed in my stomach, liver and bile. In December of 2010 I introduced Advil along with Actos and IV Zithromax. I

noticed a reduction in brain fog, but it did not help my sleep at all. During those short periods of sleep, the sweating around the head and neck returned in intensity with the Advil ?????? Look closely at the discussion at the University of Illinois, at Chicago about treating Alzheimer's patients with Actos and Advil (this could give clue about increase in sweating around head and neck with Advil).

In February 2011, I introduced the drug Meridia, 15mg, once a day, for 5 days and noticed an improvement in cognitive function caused by LD. Out of desperation, because I was still not functioning from LD, I started to use Alpha-Stim in June of 2011. After a few days it improved my cognitive impairment caused by LD, however it did little to improve my hyperhidrosis or insomnia. Alpha-Stim did eliminated the sweating at night, caused by LD, while I slept???? If I truly suffered from an anxiety disorder the Alpha-Stim should have improved my hyperhidrosis and insomnia, but it improved my condition very little, if at all. Even as I increased Alpha-Stim one hour, three times a day. As of June of 2011 my sweating is about the same as before I contracted LD in 2005 (except when I perform psychical labor, it is worse), however my insomnia is a major problem because I only average 2-3 hours of sleep per night. I still experience cognitive dysfunction and bouts of extreme fatigue. It usually starts with a sore throat, followed my cognitive impairment and extreme fatigue, this usually lasts from and hour to a few days.

On January 14, 2013 I started Hyperbaric Oxygen Treatment (HOT). For the first few days I noticed my sweating had improved, especially under my underarms and had no body odor (almost similar to the first few days I started antibotics treatment back in 2008). But soon as I was exposed to stress, the LD was reactivated and sweating and body odor returned. During the entire treatment period I would experience some positive results, but my LD would be always be reactivated under any stressful situations. On February 10th I started Actos and continued it until the 22nd. I noticed an improvement in my sweating in the first few days again. I then started Meridia on February 13, 14 and 15th; then again on February 18, 19, 20, 21 and 22. In beginning of March I noticed my LD would not be as intense, I believe this was a result of the Actos and Merida. I noticed an increase in sweating and body odor under my underarms, had returned with the Meridia ???????

I believe the main reason why I cannot shake LD from my mind is that I am processing heavy metals into a more toxic form.

Prior to LD, all my blood work over the years has basically been normal, from glucose tolerance test to thyroid function. However, A few things have been found in my blood work that could offer a clue into the cause of hyperhidrosis. Lab results found: slightly above normal limits of 24 hour urine of VMA, Methaphrine, NA, NE and DA (I believe these slightly above normal limits are trying activate CREB during times of stress), no tumor of the adrenal glands, normal free fatty acids levels, high levels of DHEA, high levels of cholesterol (good and bad), normal testosterone, slight elevation of the amino acid Histidine, all other Plasma amino acid profile normal (urine not performed), slight elevation in urine Creatinine osterone levels on the low side (except when I contracted LD), and C-reactive protein is close to zero.

During my battle with LD extensive blood work was performed to rule out any other diseases, and the lab results revealed: nuclear stress test normal, MRI of the abdomen indicated no tumor of adrenal glands, normal whole blood nutrients and potential toxic elements, 24 hour hepatocarboxyl porphyrin 6 H, hexacarboxyl porphyrins <3, coproporphyrins 25 H, with normal or negative uroporphyrins, pentacarboxylporphyrins, coproporphyrin III, (Porphyria specialist indicated I did not have Porphyria), Also, methylenetetrahydroflote **MTHFR mutations**, C677T and A1298C; **a single copy of C677T mutation was found**. C677T mutation, in the **MTHFR gene**, can cause elevated homocysteine levels in individual suffering from insufficient folic acid (I take vitamin B complex every day). Also, PQI-1 gene polymorphism, one copy of the 4G allele and one copy of 5G allele, also known as 4G/5G genotype of plasminogen activator inhibitor type 1 (PAI-gene). PAI-1 gene increase risk of coronary disease, venous thromboembolic disease, possibility complication of pregnancy, such as recurrent abortions. Tested for Human Leukocyte Antigen Typing (HLA), DRB, DQB typing: Test results, DRB1: 0301, DRB1: 0701, HLA DQ: 02GM, DRB3: 01XX, DRB4: 01ARYE; nothing for DRB5. Chromagranin A, normal.

There has been a case of a girl who had MTHFR deficiency with increased neurotoxicity of arsenic, could there be connection with my MTHFR mutation and arsenic, or another heavy metal, being processed in a more toxic form?????

Sleep study was performed on August of 2007 at Centerstate Medical Center in Freehold, NJ, because my insomnia was unmanageable due to undiagnosed, continuing effects of LD. The sleep center diagnosis

me with mild obstructive sleep apnea syndrome- 327.23. During the treatment phase, in the report, it stated that I spent 25% of the time in stage 1, 56% in stage 2, 4% in stage 3, and 0% in stage 4 and 14% in REM sleep. During the study 122 arousals were identified with no periodic limb movements present. I remember while the technician was putting the sensors on my head, I started to sweat profusely and consequently felt embarrassed and had a panic attack. The panic attack caused every pour on my skin surface to open up and I became drenched in perspiration. I did not sleep well the entire night. I remember being in a transit sleep most of the night. An observation my wife noticed when I sleep, prior to LD: she stated, when I am in a sleep state that I lightly scratch my nose and forehead. This last for a few minutes at a time where it appears I am in a sleep state. Sometimes, but not all the time, I remember scratching my facial area upon waking in morning.

Prior to developing LD in 2005, I have observed many interesting occurrences that might offer a clue into why I suffer from hyperhidrosis. Some of the below mentioned items might be trivial or funny, but I believe the human body telegraphs important messages and clues about what is wrong with us. The observations that I have noted include: short term memory problems my entire life (increase in stress drastically impairs short term memory function), difficulty processing information from short term memory to long term memory, good long term memory function (increase in stress impairs long term memory), sometimes have difficulty spelling words/forming proper sentence structure, sometimes have difficulty pronouncing certain words, in school performed better in math than English, hard time remembering words to songs (even if I heard the songs multiple times), hard time describing/remembering what I watched on TV and describing what I saw to another person, excess ear wax, greasy face, gums bleed easily when brushing my teeth, at night while I slept, and for no apparent reason during day (this stopped when I started taking vitamin supplements. I ate a normal diet during that period of time when my gums bleed-drank allot of orange juice and was a social drinker on the weekends), hyperactivity traits occurs only under stressful situations, increase sensitivity to pain only under stressful situations, indecisiveness, irritability (especially when I was younger), as a teenager stressful situations caused dramatic increase in acne, sometimes experience a loss of balance for no apparent reason, engaging in unusual/different activities results an increase in sweating, I produce above average saliva, powerful craving for sugar, paradoxical reaction to many prescription medication, experience an amphetamine like response in social situations, hands and feet feel cold under stressful situations (because an increase in sweating), repetitive/sometimes negative thoughts, I received dental fillings around the age of 19 (my condition began between ages of 12-13), during the act of sex I do not sweat, sensitivity to aspirin as a child (Reye Syndrome, intense hallucinations), developed abnormal amount of colds as a child (especially bronchitis), developed coxsakie virus around the mouth as a child, heart murmur as a child, cried allot as a small baby (especially after drinking milk based formula), persistent colic as baby, **sensitivity to hydro carbons/paint as a child (Multiple Chemical Sensitivity, develop rash on hands if I came in contact with paint or glue**), I slept with the lights on as a child because I was afraid of the dark, hyper aroused in the morning, sometimes/rarely experience smell chemical sensitivity, **stomach irritation to garlic** (develop severe acid reflux {I almost coked on the acid reflux, could not breath, on the acid reflux while I slept at night} a few hours after dinner this usually occurs, while laying down on my back, or when I am trying to sleep), in 2011 developed sharp pain in gallbladder area (usually occurs at night, while I am trying to sleep, when I role on my right side and after I ingest **garlic**), I produce a allot of gas after every meal, have trouble holding my breath under water (limited lung capacity, especially under stressful situations), strong empathy/sensitivity for people/animals and brief periods of exercise reduces my sweating temporarily.

Other important examples are: intense physical work or exercise over a long period of time, triggers racing thoughts (my mind does not want to shut down), which in turn prevents me from sleeping at bed time. Any type of physical work outside on a hot summer day causes a dramatic increase in sweating, forcing me to drink in excess of a gallon of water. In theory, this type of activity of drinking large amounts of water and sweating should detoxify my body of any unwanted toxins, but not for me. Maybe the excess consumption of water during a hot work day dilutes chemicals inside of my stomach, causing it to produce more harmful toxic chemicals at night, thus preventing me from sleeping. Any mental or physical stress during the day prevents me from sleeping at night. At the age of 16 I had an operation to fix a broken nose that occurred at a much younger age. In the middle of the operation I came out of the anesthesia, and I saw the surgical team. The surgical team was unable to put me back under the anesthesia, and the operation could not be completed. After the operation, in the recovery room, I became extremely restless and could not stop moving in the bed (I wanted to jump out of my skin. **Theory: could this usual side effect from the anesthesia be a withdraw effect, of the more toxic form of heavy**

metals, from the pituitary gland. The source of the more toxic form of heavy metals, contained in food and water, was eliminated for a period of time. It would similar to a drug addict not receiving his daily drug intake). I am not sure what type of anesthesia I was given during the operation, I think it might have been Sodium Pentothal (prior to operation I had an **empty stomach**, which may have contribute to me coming out of the anesthesia). Under stress I tend to breathe out through my mouth and not through my nose (breathing is shallow). My nose grows slightly under stress and becomes smaller when I am in a relaxed state (my wife confirmed this, so I am not crazy)(this might be indication of high levels of the more toxic form of arsenic or heavy metal in the Pituitary Gland during times of stress). After I experience intense stress for an extended period of time, I notice a substantial decrease in sweating at the end of the day, but I am unable to sleep for days. Any type of hot food triggers cranial hyperhidrosis, especially under stress. Under stress I can feel my skin temperature increase, but body temperature seams to decrease. If I am feeling the everyday "blues," on that particular day, I notice I sweat less on that day and sleep better at night. At the age of 25 I noticed a funny looking stain in the front part of my underwear. This stain is present in all of my underwear and the discharge from my penis continues to this day. The stain looks like faded dried blood, and if I shine a black light on the stain in turns purplish or maroon in color (urologist and other doctors are clueless about this. Maybe the funny looking stain is H2O2?????). I go to bathroom 1 to 2 times a day (normal bowl moments). I develop intense knife stabbing pain in my ears when a plane is descending to land. Occasionally developed slight jerking of muscles and limbs.

On rainy days, I notice I sweat substantially less. The closest medical evidence I have to support why this occurs is called Serotonin Irritation Syndrome. Scientist have attributed this to the positive or negative ions present in the earth's atmosphere during atmospheric storms. These positive or negative ions in the atmosphere seem to have an effect on serotonin levels in the brain. The positive or negative ions must be decreasing serotonin levels in my brain, thus decreasing my sweating.

One other bizarre observations has occurred repeatedly when I consumed large amounts of alcohol. After a night of drinking, I would shut my bedroom door and windows. At that time I had installed a carbon dioxide detector in my room. After a few hours of trying to fall asleep I noticed I would set off the carbon dioxide detector. This never occurred if I did not consume alcohol.

Another important observation occurs with my sweating. In the morning, especially at work, performing manual labor, there is a substantial increase in sweating in the first few hours. Also, on Monday morning's I notice a substantial increase in my sweating compared to the other days. Is it possible I am storing more toxic forms of arsenic or heavy metals over the weekend, and I am not burning these substances off during the weekend, resulting in an increase in sweating on Monday morning ???

On January of 2012 I performed an experiment where I ate the same dinner each night. However, on the first night I did not sleep at all. On the second night a large snack. An hour and half before bedtime I consumed a half a bag of peta chips, special K meal protein bar (chocolate and peanut butter), and two cookies topped with peanut butter and slice of buttered toast. The second night I slept about 5 hours (which is allot for me). The next day I also felt more relaxed in the morning. There must be some connection between the digestive tract, especially the liver, and my brain. Or some toxic substance is being secreted by my stomach and is effecting my brain. Did I accidentally increase bile acid by consuming large amount of food???????

In Dr. Daniel G. Amen book, "Making a Good Brain Great," pages 32-48, he developed a checklist for people who cannot get a brain scan to help predict areas of strengths and weakness in areas of the brain. The areas of the brain he asked question on are the: Prefrontal cortex, Anterior Cingulate Gyrus, Deep Limbic System, Basal Ganglia, Temporal Lobes (TLS), and Cerebellum. When I answered the questions in his book it indicates I am effected by some, but not all, of each area of the brain, listed in previous sentence. Dr. Amen describes treatments for specific areas of the brain, both vitamins and medication, and I have tried all of his recommendations that are listed in his book, with no success. In Dr. Daniel G. Amen book, "Magnificent mind at any age," he described and categorizes different types of mental illness and treatments. He states there are 6 types of ADD, 7 types of anxiety and depression and I can state that I could fall into some, if not all of some aspect of the 6 types of ADD and 7 types of anxiety and depression. However, I only fall into these categories if I am under stress, going to be under stress, and after experiencing stress over a period. If I am not under stress I do not fall into these categories listed in Dr. Amen book. There has to be something more to my metabolism that causes me not to truly suffering from ADD, depression or anxiety ?????

Published in Neurology 36, March 1986, 378-381, entitled "Obsessions and compulsions in Gilles de la Tourette's syndrome. Dr. Frankel discusses how OCD is a prominent feature in approximately one-half of

the cases of GTS. On page 380, there are a list of questions for OCD inventory and I can say I answered most of them with yes. I only answer yes to these questions when I am under stressful situation or I am going to be under stressful situations. Under non stressful situations I would not answer yes to most these questions.

Published in Journal of Consulting and Clinical Psychology, 1969, 33, No. 4, 448-457, entitled "Measurement of Social- Evaluative Anxiety. Dr. Watson developed two scales Fear and Negative Evaluation scale (FNE) and Social Avoidance and Distress scale (SAD). People with high SAD tended to avoid social interaction, preferred to work alone, reported that they talked less, were more worried and less confident about social relationships, but were more likely to appear for appointments. Those high in FNE tended to become nervous in evaluative situations, and worked hard either to avoid disapproval or gain approval. On page 450, there is a list of questions for SAD and FNE and I answered yes to most of these questions. Yet again, stress or my interpretation of stress, plays a major role in answering yes to these questions.

Also, everything is stressful in my life. For example, if I change a light bulb I will start to sweat within a few seconds. Even writing this paper causes a dramatic increase in my sweat rate under my under arms. However, most of the time, I have not let things stop me from doing most things in life, even though I am very uncomfortable and do not truly enjoy it.

In conclusion, I believe strongly that hyperhidrosis is a stress disorder. In 1997 when I first meet my wife, it was the first time I had someone in my life (My condition developed in 1978-79 between the ages of 12-13, in 1985 I had my first dental fillings). During the first year of our relationship I noticed my sweating and insomnia improving, in some cases significantly (however, under intense stress no difference). As soon as or relationship developed and grew, as I tried to led a normal life, my hyperhidrosis and insomnia returned in intensity (in some situation it became worse, especially the day of my marriage and soon afterwards).

I have tried over 80 medications since 1985 for hyperhidrosis and insomnia. I've tried prescription medication because I exhausted all other forms of therapies. I can state that all of the prescription medication I have tried have mostly failed. The same side effects are present in almost every medication I've ingested: I experience an increase in insomnia (I usual experience amphetamine like effect), dry mouth, hyperhidrosis increases and I develop severe constipation. This is only a partial list, but it gives the reader examples of how different drugs have interacted with my metabolism. For example, **Prozac (Fluoxetine),** a Select Serotonin Reuptake Inhibitor; after 6 weeks of taking this drug my sweating under my underarms increased tremendously. It helped relieve my sweating around my face about 50%. I developed insomnia (wired), severe constipation and dry mouth. All SSRI's prevented me from ejaculating. In theory, Prozac should have cured me of my disorder since it increases the level of CREB through serotonin. My CREB is set in stone and will not move. In laboratory animals serotonin increase levels of CREB in these animals. I believe it did not work for me, because I am already producing above normal limits of serotonin (in times of stress), as it is trying to activate CREB. Anti-depressants increase CREB in hippocampus and cerebral cortex, but not in nucleus accumbens or locus ceruleus. **Garbitral,** a GABA reuptake inhibitor; I experienced insomnia (wired) and increase sweating. **Diphenhydremine,** inhibits reuptake of serotonin; I felt groggy, sweating increased, dry mouth, racing thoughts and insomnia. **Valium,** benzodiazepines; increase sweating, wired, anxiety ridden. **Scopolamine,** anticholinergic, antimuscarinic, completive antagonist at muscarinic acetylcholine receptor antagonists, specifically M1 receptor; increased sweating, dry mouth; this drug suppresses CREB. **Carbamazepine**, tricyclic anticonvulsant, developed rash, no effect on sweating or insomnia. **Campril**, blocks glutamaterigic, NMDA receptors activates GABA receptors; I was wired big time, substantial increase in sweating. **Remeron,** tetracyclic antidepressant, it increases NE and 5-HT; I was wired big time, increased sweating, insomnia. **Topiramate,** increased sweating, wired, could not sleep, felt and acted stupid (under the treatments section, this drug helped some patients with hyperhidrosis and psoriasis). **Amitripyline,** serotonin and norepinephrine uptake inhibitor; increased my sweating, wired big time, no sleep. **Requip**, dopamine agonist; increased sweating, wired big time, no sleep. **Statera,** a selective norepinephrine reuptake inhibitor; I was wired big time, increased sweating. **Risperdal**, monoaminergic antagonist; I feel asleep for one hour, then it felt like someone injected me with adrenaline, minimal improvement in sweating. **Riluzole** antiglutamatergic agent (reduces gluatamatergic/blocks glutamate), blocks calcium and sodium channels and blockage of GABA; increased sweating under the underarms, could not sleep at all, not wired just could not sleep, cognitive function impairment. **Zyprexa**, antipsychotic agent is

combination of dopamine and 5HTP type 2 (5HTP2) antagonism, antagonism of muscarinic M1-5 receptors, antagonism of histamine receptor; I took it for over year, because I was desperate for sleep, not knowing I was still suffering from the continuing effect of LD and had a lesion on my brain stem. When I stopped taking Zyprexa I suffered through three months of withdrawal and out right hell (significant increase in sweating and no sleep). At one point I thought I was going to die and my heart explode inside of my chest because **I did not sleep for one second over 7 straight days**. At that point had to be put on **Fazaclo** (clozapine) so I could fall asleep. I experienced Serotonin Syndrome when I withdrew from Zyprexa. According to The New England Journal of Medicine, serotonergic neurons in the CNS are found primarily in the midline raphe nuclei, located in the brain stem from the midbrain to the medulla. The rostra end of this system assists in the regulation of wakefulness, affective behavior, food intake, thermoregulation, migraine, emesis, and sexual behavior. The neurons of the raphe in the lower pons and medulla participate in the regulation of nociception and motor tone. In the periphery, the serotonin system assists in the regulation vascular tone gastrointestinal motility. Also, physical activity would result in a substantial increase in my sweating while on Zyprexa. **Lyrica**, anticonvulsant drug, binds to alpa2 delta sites, increase density of GABA transplant but it does not bind directly to GABA; I fell asleep for one hour and then awoke with my mind racing, increase sweating. **Meridia** produces therapeutic effects by norepinephrine, serotonin and dopamine reuptake inhibition. Meridia and its major pharmacologically active metabolites (M1 and M2) do not act via release of monoamines. Meridia pharmacological actions predominantly via its secondary (M1) and primary (M2) amine metabolites. The parent compound is a potent inhibitor of serotonin (5-HT) and norepinephrine; norepinephrine reuptake in vivo, but not in vitro. However, metabolites M1 and M2 inhibit the reuptake of these neurotransmitters both in vitro and vivo. This drug made me wired, I could not sleep, I developed a dry mouth and my sweating increased. However, after about 3-4 hours after taking the Meridia I become sleepy, but this last only for ½ hour or so????? **Lexapro**, SSRI reuptake inhibitor; It increased anxiety, could not sleep. **Abilify,** antipsychotic, antidepressant; I was messed up, out of it, could not sleep, increased sweating. **Propranolol**, non-selective beta blocker, it blocks the action of epinephrine and norepinephrine on both B1 and B2 adrenergic receptors; It increased sweating under my arms and feet, increased overall sweating, and increased insomnia. All sleep aids on the market today prevents me from sleeping, for example the drug **Ambien,** short acting no benzodiazepine hypnotic that potentates GAGA; it took about 2 hours before a felt sleepy. I fell asleep for 20 minutes, then it felt like someone injected me adrenaline. The next day I felt horrible, physically sick. **Carnitine,** vitamin supplement, increased sweating, increased insomnia, anxiety, and felt pumped up. **Ginkgo Biloba, vitamin supplement, mind raced out of control. I experienced intense obsessive, useless thoughts (Dr. Amen stated the best looking brains, that he tested, on the SPECT scan, took Ginkgo Biloba. All his patients felt better on Ginkgo Biloba; it makes no sense why I would have such an usual side effect ???) BuSpar**, increased sweating, could not sleep. **Nightquil** (taken while I was sick), cold suppressant; stimulant effect, my mind raced out of control that I could not sleep one second. My mind would not shut down for one second (I thought someone injected adrenaline into my bloodstream), increased sweating and insomnia. The vitamin supplement **Enula** (nutramedix, main ingredient is Inulin) increased gallbladder discomfort and pain??? **Baking Soda** 1 tablespoon in a glass of water, empty stomach was a stimulating effect. **Phosphatidylcholine, increased my sweating and insomnia significantly (it was a stimulant)**.

Before I go any further let me talk about the weight loss drug **Meridia**. The drug Meridia is used by Dr. Mueller of Princeton, NJ as a cure for PTSD (before the FDA pulled off the market). Dr. Mueller and his colleagues performed a small study at Beth Israel Hospital, in Newark, NJ, and published their findings in Epilepsy and Behavior. Dr. Mueller also received a use patent for the drug Meridia, it is patent no. US 6,323,242 B1, Date of Patent Nov 27, 2001, which lists in great detail the effectiveness of this drug. The independent findings performed at Beth Israel resulted in a 90% success rate for suffers of PTSD. He also uses Meridia for successful treatment of violence, self-laceration, repair of altered sexuality, ADD, OCD, Tourettes Syndrome, relief of hyposexuality, Huntington‘s Disease, Intracerebral and Porencephalic Cyst with Oscillopsia, Fibromyalgia, farsightness, hearing impairment and heroin craving and abuse. I have spoken and met some of his patients who miraculously have been cured of there PTSD, Fibromyalgia and Tourette’s syndrome with Meridia. I could not believe what his patients told me about their recovery from their PTSD with Meridia, except it was a miracle. The drug works within 10 to 15 minutes and soon these patients find relief form their PTSD symptoms. After a few months of treatment they are cured of this disorder. One very interesting side effect of this weight loss drug that occurred in the majority of his patients is that they gained a substantial amount of weight from this drug. Which is very odd since

Meridia is a weight loss drug. When Dr. Mueller brought this drug to my attention I thought Meridia could possibly be a cure for hyperhidrosis. Since I suffer from a stress disorder, and PTSD is one of biggest stress disorders of them all. Meridia, in theory, should have worked for me, but it did not. The reason why I believe it did not work for me, is prior to these people developing PTSD they were healthy normal people who are capable of activating and maintaining their CREB levels. When these patients developed PTSD, the CREB protein was temporarily dephosphorylated, or deactivated. When these individuals ingested Merida it somehow shocked the CREB protein back into sequence, just like a heart attack victim receiving defibrillator treatment to jump start the heart. Since I am unable to activate and maintain the CREB protein at a higher level, the drug was ineffective. I believe I produce a natural Meridia in my body already, and that everyday my HPA axis is trying stimulate the CREB protein (in times of stress) through higher levels. The HPA axis is elevated in times of stress because it is performing a type of neuro-genesis every day. This neuro-genesis causes H2O2 to develop. I believe many of the psychiatric drugs on the market today are ineffective because my body is already producing higher levels of many of the neurotransmitters contained in these drugs. It is similar to putting water, into a glass already filled with water.

Medications and Vitamins that had some positive effect on my condition: **Alcohol,** depletes DA and 5HTP, and increases GABA. Alcohol activates the CREB through PKA, CaMK pathway. After about 3 beers my sweating decreases, depending on the social situation. However, I cannot sleep at all, and it makes me wired (my mind does not want to shut down). I also noticed I have a very low tolerance for alcohol, even after years of being a social drinker. **Namenda,** activates NMDA by excitatory amino acid glutamate, antagonistic effect on 5HT3; almost the same effect as alcohol, but not drunk, sweating decreased for only a brief period of time, increased insomnia. Namenda increases the CREB protein. **Aricept,** enhances cholinergic function by increasing acetylcholine, increases cortical acetylcholine (inhibits acetycholinesterase); it decreased sweating for only a brief period of time, and had a similar effect as Namenda. **Methylpredniosolone,** (taken in 2007) for herniated disk in neck (caused by LD and football injury). It was one of the best medications I have every taken, improved overall condition. I took the medicine for 5 days, and after about 2 weeks experienced one day of severe withdrawal, felt weak and tired, blood pressure dropped to 120/40. After I stopped taking this drug, I noticed my symptoms of LD returning; especially the extreme fatigue and insomnia. This drug suppresses the immune system and I should not have taken this drug, but I did not know I was still suffering the effects of LD. This drug retriggered my LD. **Clonidine,** a presynaptic Alph2 receptor in the vasomotor center of brain stem, it decrease presynaptic calcium levels and inhibits NE; it was one of the few drugs that improved my hyperhidrosis for a short period of time, but it did not improve my insomnia (it made me sleepy, but I was in a transit sleep the entire night). However, I felt very lethargic, and I built a tolerance to the drug over a period of time**.** When I took it again in 2007 (still unknowingly feeling the effects of LD) it did not improve my condition at all. Clonidine have been reported to decrease LC firings in animals and reduce anxiety in man. **NAC**-**Acetylcystein**e, monolithic agents, oral; first few days I took NAC it improved my sweating and sleep. I slept 8 hours the first two nights (since the age of puberty I have only slept 8 hours per night a handful of times). I also could not go to the bathroom for over a week (severe constipation), even with a prescribed stool softer (this side effect is highly unusual). **I developed unusual paranoid thoughts, after a week on NAC (I believe now that the toxic form of arsenic or a heavy metal was being redistributed to another part of my brain);** and the NAC treatment became ineffective**. DHEA,** helped a little bit with my condition but I developed intense headaches. **Testosterone**, made me feel great for a period of time, helped sweating around face and hands, and helped a little with my insomnia. **Pepto bismol and Tagment**, after about 30-45 minutes it makes me so sleepy I cannot keep my eyes open (I did not fall asleep, just made me sleepy), soon afterwards my mind does not shut down. Scientist have found that Pepto bismol reduces odor with excess gas. The component that gives gas its offensive odor is HS2 produced by bacteria in the intestine. The reason for Pepto bismol is so effective for flatulence and gas is its Bismuth component. Bismuth binds to H2S produced by intestinal bacteria and prevents it from being released in gaseous form (Bismuth Subgallate-Devrom). In the Canada Journal of Gastroenterology, October 2007, 21(10) 665-667, Doctors gave IV fluids and IV pantoprazole, 40 mg twice per day for a man who inadvertently ingested 250 mL of unlabeled Hydrogen Peroxide. There are three main mechanisms of toxicity from Hydrogen Peroxide, caustic injury, oxygen gas formation and lipid per oxidation. **Phosphatidyserine (vitamin supplement**) I noticed improvement in my sweating, lasting about 2 hours. It causes insomnia, even if I take it in morning. In addition, I developed angry thoughts and became angry and nasty in everyday situations (taken in 2007, LD) (somehow this vitamin has an effect on

CREB in published medical journals). **Omega3 fish oil and Bioflavonoids**, had a 10% positive effect on my sweating and insomnia. **Actos**, had a positive effect on my immune system and also some positive effects on my sweating while I was afflicted with LD and eliminated my fear of heights. **Cholestyramine**, cholesterol lower agent, bile acid sequestrant, which binds bile in the gastrointestinal tract to prevent its re-absorption; it decreased my sweating under my under arms by 10% and decreased sweating around face and hands by 50% in social situations, but after a period of time (over a week) the Cholestyramine had limiting effect. It also increased my insomnia and I developed NO constipation. Cholestyramine is used off label for the treatment of Irritable Bowel Syndrome. In my case it caused an increase in the number of times going to the bathroom. For the first time in December of 2011 notice gallbladder discomfort after taking Cholestyramine. **Pillsbury Cinnamon Rolls (PCR)** (contains 10g of fat)**,** if I eat a whole roll of PCR at night, sometimes, not all of the time, I get 8 hours of sleep (prior to LD). I have only received 8 hours of sleep a handful times since the age of puberty.

All oral antibiotics had a positive effect on my condition before developing LD in 2005, now they have an amphetamine like response; after about an hour I start to sweat, heart races slightly and I am wired (cannot sleep) (there is one exception to this, in the beginning of October of 2008 when I was first diagnosed with the continuing effects of LD, I was given oral antibotics and noticed a substantial improvement in my insomnia and sweating; but it only lasted a few weeks). This is because the antibiotics are attacking the LD bacteria and the Lyme bacteria is releasing neurotoxins into the bloodstream (Herxhemer Reaction). Antibiotics also caused knife stabbing pain in my gallbladder while I was dealing with LD. This occurred after a year on oral antibiotics. Scientist have recently discovered that minocycline hydrochloride (tetracycline) a drug that inhibits H2O2 by generated by neutrophils (white blood cells, are the first responders of inflammatory cells to migrate toward inflammation) showed a decrease in the ability of neutrophils to produce H2O2 (this might explain the positive effect of antibiotics on me prior to LD). The antibiotic, **Sulfameth**, I noticed briefly an improvement in my condition. However, I noticed a **substantial increase in the number and volume of urine I produced at night at the start of using the medication ???**

After I eat a large high protein meal (3-5 eggs) and take a multiple vitamin, flavonoid, Omega 3 fish oil, etc. I noticed after an hour I feel sleepy and fall asleep for an hour. During this time I can feel my body temperature drop (I fell cool), but this only last about an hour. Also if ate a large dinner, where I am stuffed and bloated (especially St. Patrick day, maybe the **boiling** of the meal detoxifies the food of heavy metals, especially arsenic), **I noticed 45 minutes afterwards I notice a reduction in sweating and feel more relaxed**. Also, after I eat a protein meal, my brain feels more "relaxed" (less hyper aroused).

MSM Sulfur, 1000mg of MSM and 300 mg of Sulfur. I noticed a reduction in sweating by 20% in non-psychical environments.

The amino acids, **Arginine** 500mg **L-Glutamine** 500mg and **Glycine** 500mg, helps a little with my insomnia. The amino acid **Tyronsine** 500mg increases my sweating and makes feel pumped up???? The amino acid **L-Tryptopan** helps a little with my insomnia and makes me feel relaxed, sometimes. If I take Tryptopan before dinner it makes me sleepy at night, sometimes. If I take Tryptopan after dinner it prevents me from sleeping??????? Also, have a hard time ejaculating. When I stopped taking Tryptopan I suffered from withdrawal and could not sleep for 3 days (all amino acid where taken in end of 2011). In conclusion, I have noticed that I am very sensitive to any medication and vitamins.

The vitamin supplement Zeolite, by NutraMedix (it has similar to cat litter) taken every third day improved my insomnia (get 5 hours, which is allot for me). After a few treatments insomnia returns.

Published in the American Journal of Physiology-Gastrointestinal and Liver Physiology. Entitled, "Stomach-brain communication by vagal afferents in response to luminal acid back diffusion, gastrin, and gastric acid secretion 2004 Mar, 286(3):g403-11. Dr. Danzer and team found that the vagel afferents play a role in gut-brain signaling of physiological and pathological stimuli. They investigated how backdiffision of luminal HCL or NH4OH and pentagestrin-stimulated acid secretion interact in the communication between rat stomach and brain stem. Rats were pretreated intraperitoneally with vehicle or appropriate doses of cimetidine, omeprazole, pentagastrin, dexloxiglumide (CCK1 receptor antagonist), and itriglumide (CCK2 receptor antagonist) before intragastric administration of saline or back diffusing concentration of HCL or NH4OH. Two hours later, neuronal activation in the nucleus of the solitary tract (NTS) and area postrema was visualized by c-Fos immunohistochemistry. Exposure of the rat gastric mucosa to HCL (.15-.5 M) or NH4OH (.1-.3) led to concentration dependent expression of c-Fos in NTS, which was not related to gender, gastric mucosal injury, or gasropyloric motor alterations. The c-Fos response to HCL was diminished by cimetidine and omeprazole, enhanced by pentagastri, and left

unchanged by dexloxiglummide and itriglumide. Pentagastrin (when given intravenously it causes panic attacks, from the internet) alone caused an omeprazole-resistant expression of c-Fos, which in the NTS was attenuated by itriglumide and prevented by dexloxiglumide but in the area postrema was reduced by dexloxiglumide and abolished by itriglumide. We conclude that vagal afferents transmit physiological stimuli (gastrin) and pathological events (back diffusion of luminal HCL or NH4OH) from the stomach to the brain stem. These communication modalities interact because, firstly, acid secretion enhances afferent signaling of gastric acid back diffusion and secondly, gastrin activates NTS neurons through stimulation of CCK1 receptors on vagal afferents and of CCK2 receptors on area postrema neurons projecting to the NTS. Also, Helicobacter pylori urease has been found to cause gastric inflammation and injury and to modify the ph-dependent regulation of gastrin and gastric acid secretion.

Before I go any further, let me elaborate on the diabetes drug **Actos** (Actos activates AMPK liver enzyme. It also enhances glucose uptake, increase fatty acid oxidation and decrease absorption of glucose from gastrointestinal tract. It decreases heptic glucose production, decreasing intestinal absorption glucose and improves insulin sensitivity {increase peripheral glucose uptake utilization}. It is an agonist for PPAR gamma receptors. PPAR gamma receptors modulates the transcription of number of insulin responses genes involved in the control of glucose and lipid metabolism. It enhances the effects of circulating insulin, by decreasing insulin resistance, it does not lower blood glucose. Actos decreases free fatty acid in low and high fat diets. An increase in insulin causes a decrease in free fatty acid. Norepinephrine excess causes insulin resistance {increase insulin}. In insulin resistance requires the body to produce more insulin, and the body does not properly use it.) Listed in the PDR, about Actos, it states," Actos is extensively by hydroxylation and oxidation; the metabolites also partly convert to **glucuronide(Glucuronidation is the conversion of chemical compounds to glucuronides, is a method that animals use to assist in the excretion of toxic substances, drugs of other substances that cannot be used as an energy source) or sulfate conjugates**. This might explain why Actos had a positive effect on my hyperhidrosis. The Actos was somehow processing or getting rid of the more toxic form of arsenic or other heavy metals.

During my battle with LD, oral antibiotics did not improve my condition. In fact, I was getting worse. In a desperate measure I tried **Actos** on my own and within one week I noticed an improvement in how I felt. The first 48 hours I did not sleep one second and experienced and amphetamine like effect (prior to taking ACTOS I AVERAGED 1 HOUR PER NIGHT). Prior to taking Actos my immune system was greatly suppressed by LD. My immune system was similar to someone who had full blown AIDS. This was proven with a blood test called CD57 striker panel, which tests the strength of the immune system. Within three months of treatment with Actos my immune system returned to normal levels, which was proven again with the CD57 striker panel blood test. This is highly usual, and I have not found this type of positive effect produced by Actos in any published medical journal. It even surprised the Dr. Eiras who was treating me for LD. I believe Actos shuts down the flow of Free Fatty Acids (FFA) or helped remove excess toxins from the liver. In a publication I read on the internet, by Dr. Shoemaker, Maryland, USA, theorized that all LD bacteria hide in the fatty tissue of the hosts. If that is the case, then Actos must have forced the LD bacteria hiding in the fatty tissue into my blood stream, by shutting down the flow of FFA. I believe my immune system was not suppressed like someone afflicted with the AIDS virus, but it was just tired trying to find the organism hiding in the fatty tissue. When the Actos shut off the flow of FFA the LD bacteria started to starve, and was forced into my bloodstream where my immune system was waiting. Simply, the Actos could have reduced inflammation in my brain. Another theory is Actos somehow indirectly effected the CREB protein and boosted my immune system and decreased inflammation in my brain. I believe I would have improved at a much quicker pace with the Actos, but at the same time I was also taking **Heparin** with oral antibiotics. Some doctors who specialize in LD give Heparin along with antibiotics. I found out from Dr. Mueller Heparin increases the flow of free fatty acid, so in a sense I was canceling out the effects of the two drugs (Actos and Heparin). As soon as I stopped taking Heparin my immune system improved at a much faster pace (proven again with CD57 striker panel test, labcorp).

Published in Medpage today (on the internet), June 4, 2009, "Metformin Boosts Immune System in Mice, "found Metformin boost the long term memory in mice. The scientist found Metformin increase CD8-postive memory T cells that maintain the long term immune response, Dr. Choi and colleagues reported in the June 4, "Nature." Indeed, in one experiment, the increase in so-called CD8 Tm cells translated to a survival advantage when mice were challenged with an experimental tumor cell line, Dr. Choi and colleagues reported. "Our findings were unanticipated, but are potentially extremely important and could revolutionize current strategies for both therapeutic and protective vaccines, Dr. Choi said. The

set of "effector" T cells vanished in time, leaving long lived CD8 Tm cells that can spring into action if the same pathogen attacks again. But exactly how that happens remains unclear, so Dr. Choi and colleagues were trying to pin down the process by studying mice deficient in their ability to produce a protein (dubbed TRAF6) involved in that initial response. The animals were able to mount a normal effector-cells response to bacterial infection, they found, but when the researchers measured Tm cells 60 days later, there were significantly fewer that in control animals. Further study showed that T cells missing the TRAF6 protein also had defects in fatty acid metabolism. Specifically, the T cells couldn't make the switch from burning glucose-a characteristic of proliferating cells-to other methods of generating energy, such as fatty acid oxidation. Since Metformin promotes the activation of a protein involved in regulating fatty acid activation-AMP activated kinase, or AMPK-the researchers tested the effect of the drug. They found that injections of the drug promoted survival of T cells after bacterial infection and throughout the contraction phase, leaving a pool of Tm cells able to respond to reinfection. "We serendipitously discovered that the metabolizing, or burning, of **fatty acid** by T cells following the peak of infection is critical to establishing immunological memory," according to lead author Dr. Erika Pearce, of the University of Pennsylvania. "We used Metformin, which is known to operate on fatty acid metabolism, to enhance this process, and have shown experimentally in mice that metformin increases T cell memory." In addition, Dr. Pearce said, the drug increased the animals' responses to an experimental vaccine against a tumor cell line.

During my treatment for LD, I tried the prescription drugs **Actos** (45 mg once a day, in the morning) and **Cholestyramine** (3-4 packets per day; it has to be taken at certain times of the day because it prevents the absorption of food and vitamins). I noticed improvement in my sweating with these two drugs. Sweating under my underarms and feet only improved by 10%. The sweating around my face, hands and the rest of my body improved by 50% in casual social situations. However, if my LD was acting up, on a particular day, or I am in stressful social situations then the sweating under my underarm increases greatly in intensity and the drugs have limited effect??? After a week of treatment the combination once again had limited effect. Also, I still suffered the effects from insomnia, caused by the Cholestyramine. Any cholesterol drugs I have taken in the past has caused an increase in my sweating (underarms) and insomnia. After a week of treatment (4 packets per day), I started to develop symptoms of depression (I believe depressive symptoms are being caused by a decrease in cholesterol, which is lowering DHEA levels). These symptoms of depression occur only when I am in a transit sleep at night. Let me explain, I fall asleep at night for one hour, then for the next two hours I am in a transit sleep. During that time I have very uneasy, fearful, depressive thoughts. After a total of three hours of transit sleep, I am awake for the rest of the night. If I lower the doses of Cholestyramine (2-3 packets per day) the depressive symptoms disappear, but insomnia improved slightly. However, the drug produced no relief in sweat rate during physical work or exercise. I contacted Rutgers University School of Pharmacology about the drug Cholestyramine. They stated to me that Cholestyramine at first decreases the flow of bile acid, this then causes the liver to produce more bile acid, thus increasing bile.

One very interesting and usual observation with Actos: **Actos caused me to be less afraid of heights**. I noticed this when I was on a 30 foot ladder (usually I am very tense when I am up that high), however, I noticed when I had taken the Actos over a couple of days (on the third day) that I was relaxed or not concern about high up I was ??? Also my hyperhidrosis improved greatly??? But like usual my metabolism adjusted after about 4 days and once again the drug had limited effect. When I ingest Actos on the first day, I experience an amphetamine like response; I was awake for 2 days straight ???

On October of 2011 starting taking **Welchol**, a bile acid sequestrant, with the Alpha-Stim. Approximately 2 hours after taking Welchol I noticed I was pumped up, energized (the list of adverse reaction does not mention this stimulating effect of this drug ???). I noticed improvement in sweating and insomnia in the first few days, on the third day I slept 5 hours and my sweating was overall better. I also suffered from severe constipation. Soon afterwards my metabolism once again adjusted and the Welchol had a limited effective. I stopped the medication and a few days later tried the Welchol again, with little improvement, except I had no constipation???

In late of October of 2011 I tried the vitamin supplement "**Natural Calm**, a magnesium powered supplement," at night to help me sleep. It comes in a powder form, mix with hot water and drink (400 mg). This supplement pumped me up, (it energized me), and kept me awake most of the night, slept one hour which was in a transit sleep (I did not take with calcium???). However, the next day I noticed my sweating had improved, especially around my face ??? Also I had a hard time ejaculating. This effect I experienced was almost similar to SSRI's that I had taken in the past, except my sweating had improved (SSRI's increase my sweating). However, after a few days it had once again limited effect and under

stressful situation limited effect. **Magnesium Malate** also improved my sweating, but prevented me from sleeping at night and caused little cognitive impairment (brought out my LD).

MiraLax, over counter laxative, (contains **Polyethylene Glygol**), after a few hours I noticed my body temperature drop and felt cool. Helped with sleep, I had a normal sleep. It also made me calmer and normal, but I felt stupid (maybe the reduction in the HPA, a reduction in an amphetamine like response, is responsible for being stupid). Sweating improved, but over 5 days it lost its effectiveness. However, psychical activity increased my sweating dramatically. I also notice a substantial increase in the number of times I urinated at night and increase in the volume of urine????? Polyethylene Glycol solution passed through the GI tract to flush out, remove traces of Arsenic and prevents it from being absorbed by the gut. Published online, Open Source Clinical Toxicology Curriculum, polyethylene glycol has been shown the most efficient means of gastrointestinal decontamination in some circumstances. It may be more efficient for virtually all poisonings (through direct comparisons have been made for only a few drugs) but because of the amount of labor associated with the technique it is largely limited to some specific poisonings for which activated charcoal alone is not satisfactory. Polyethylene glycol physically flushes tablets from the gastrointestinal tract. It also increase the clearance of drugs by interrupting the enterophepatic circulation.

Arsenicum Album C200, 20 minutes after ingestation I noticed stimulating effect, increase in sweating. 3 hours later became very sleepy, but soon after 3 hours sleepiness goes away?????? **Iron** supplements 30 mg, three times a day, made me sleepy and sweated a little less.

Some of the prescription medication I have tried in the past has produced a paradoxical reaction. Dr. Mueller stated to me that I have a unique metabolism, because of the way I process prescription drugs. This might indicate that something is wrong with my stomach or liver. The list of drugs and vitamins that had positive effect either increased CREB or had an effect on my stomach, liver or bile acid.

I came across a discussion forum on the internet and someone suffering from hyperhidrosis stated they found relief from the drug called **Oxybutynin**. It is an anticholinergic, used to treat urinary and bladder difficulties. It competitively antagonizes the M1, M2 and M3 subtypes of the muscarinic acetylcholine receptor. **All anticholinergic drugs made me groggy and had no effect on my sweating or insomnia**.

Vitamins and Diet. Before developing LD I never considered vitamins or diet could be a factor in relieving hyperhidrosis. Many years ago my uncle sent me an article in a magazine where a young girl who suffered from the effects of hyperhidrosis enrolled in a health spa in Spain. The health spa specialized in strictly a juicing diet with fruit and vegetables using organic items. The diet was similar to the diet found in the book, "21 pounds in 21 days, the Martha's Vineyard diet detox" by Roni Deluz. From what I can remember from the article, she found relief from her hyperhidrosis after being on an all juicing diet for a number of weeks. At that time I was trying to find relief with prescription medication and did not have faith she would find continued success from her hyperhidrosis. I do not know if she is still not suffering from hyperhidrosis.

Not too long ago I tried a similar diet of all juicing diet using fruits and vegetables. In the morning I would have one organic egg with vitamins. Then around 9:00 am I would have a smoothie containing fresh vegetables from the local farm in the area. The farm used very little pesticides over its vegetables and I washed the items thoroughly when I got home. I only used fruit that the thickest peals from the supermarket, like oranges, pineapple and watermelon. Then I would mix the locally grown vegetables and fruits that where in season, add a little water to the blender. This produced about 2 glasses of mixture of fruits and vegetables. I usually had this three times a day, once at 9 am, 12 pm and 3 pm. Then around 5 pm I would have one organic egg. Over 18 days I lost over 20 pounds being on this diet. I had to stop because I was losing too much weight. At the end of 20 days I noticed my sweating had decreased by 50% and I felt more relaxed in non-stressful situations. **In stressful situations this diet had limited effect**. There is one major factor that affected the outcome this diet, and that is, I am still suffering from the continuing effects of LD. The diet may have worked more effectively if LD was not still altering my immune system.

Hyperhidrosis is a stress disorder and any type of stress causes a depletion of vitamins and mineral. A daily vitamin regiment should be included in anyone suffering the effects of hyperhidrosis. Since I believe there is some type of connection between psoriasis and hyperhidrosis, the book the "The Psoriasis Cure" by Lisa LeVan could be helpful for hyperhidrosis patients. The author of "The Psoriasis Cure" is a biochemist who found relief form her psoriasis, from the diet and vitamin protocol she describes in her book. The reason I say this because the drug Topirmate was successful in treating people afflicted with psoriasis and hyperhidrosis. The diet and vitamin protocol she describes in her book could possibly have a

positive effect on hyperhidrosis. My 83 old mother, who has been suffering with psoriasis her entire life, and has experienced no success with every medical treatment for psoriasis, has noticed some improvement in her psoriasis with the diet described in her book and Cholestyramine (she does not follow the diet and vitamin protocol described in her book 100%). After a week the Cholestyramine has a limited effect on her psoriasis.

For six months I tried a gluten free diet (some psoriasis suffers have found relief with a gluten free diet), no refined sugar, no high fructose corn syrup and soy based products. I noticed some, to limited effect with this diet.

Since I believe hyperhidrosis is a stress disorder, and LD is always retriggered by stress, the true effect of a vitamins, prescription medication and diet regiment may never be achieved. Now that I might have found some relief for my hyperhidrosis, the LD is preventing me from seeing the full potential of these types of treatment options. Since I am still suffering from the effects of LD for such a long time, I am starting to wonder if I am ever going to be cured of LD.

The author of the "Psoriasis Cure," Lisa LeVan (biochemist) talks about many important subjects, but one item stood out in her book. She discussed how the adrenal glands produce hormones that slow digestion down when you are stressed. When the body is not able to completely digest protein, or if your intestines are not able to absorb protein breakdown products, too many amino acids and polypeptides may accumulate in your bowels. **Bacteria in your bowels turn these into toxic compounds called polyamines**. Researchers have found lots of these toxic compounds in people with psoriasis. These polyamines prevent your body from making cAMP. When there is a lack of cAMP, the pile of scales accumulates on the skin of psoriasis patients. You need cAMP to keep your cells from going crazy and reproducing too fast.

Infection, such as candidiasis, can also lead to psoriasis symptoms. Candida albicans (a yeast like fungus) lives in your intestines and doesn't cause harm there. It is a problem when it spreads to other places. It is normally kept under control by your body, but it goes wild when you take certain medications, such as antibiotics, corticosteroids, oral contraceptives, and antacids; when you don't have enough enzymes in your digestive system; or when you eat the wrong things. The yeast can also get into your blood steam directly or produce toxins that can be even more damaging in your body. It can also decrease your body's production of cAMP, thereby causing your skin cells to reproduce too quickly.

People with psoriasis have problems with their immune systems. Poor immune function certainly appears to be a causative factor in psoriasis. Your **thymus gland** (thymus gland is involved in Fatal Familia Insomnia (FFI)) determines, to a great extent, the health of your immune system. You know you thymus gland has problems if you get frequent infections or suffer from chronic infections. If you have hay fever, allergies, migraine headaches, or rheumatoid arthritis, you probably have something wrong with your thymus gland. The thymus gland secretes a hormone called thymosin, which regulates the production and maturation of immune cells called T lymphocytes. These white blood cells give your cell mediated immunity. This type of immunity is extremely important to help your body fight yeast infection, parasites, and viruses. If you have a viral or yeast infection, your cell mediated immunity isn't working right. Your cell mediated immunity also protects you from cancer, allergies, and autoimmune disorders. **Thymic hormone levels are typically very low in people exposed to lots of stress**, AIDS patients, the elderly, and people prone to infections.

The author also explains about the pancreas not working correctly in psoriasis suffers; which can cause too little sugar in your blood (hypoglycemia) or too much sugar in your blood (hyperglycemia or diabetes). Hypoglycemia is a common problem of people with psoriasis. When the body is fighting to stabilize blood sugar levels, it can't focus on proper digestion. Digestion is vital to proper elimination of toxins. If toxins are allowed to build up in the body, they can cause such problems as inflammation and uncontrolled cell division, which of course, leads to the problems of psoriasis. You can easily recognize symptoms of hypoglycemia. If you are agitated or irritable when you wake up in the morning or before meals, and then feel much better after eating. If the answer is yes, then you have discovered one of the underlying causes of your psoriasis. She also states that your brain needs glucose to function. If your brain doesn't get enough glucose, you could lose consciousness or even die. Nature keeps this from happening by releasing a chemical called epinephrine, or adrenaline. This chemical sends more sugar into your bloodstream and raises your level back to normal. However, it also aggravated your psoriasis. NOTE: When I eat a high protein meal, especially eggs, with vitamin supplements, I notice I become more relaxed and can actually feel my body temperature drop, and become sleepy for a brief period of time.

Many of the diet books on the market today talk about detoxifying to lose weight or find relief from some underlying medical condition. These books always mention sauna as an excellent way to excrete fat soluble toxins through the skin by sweating. Dr. Colbert, in his book "Toxic Relief," talks about fasting and detoxification through diet. In his book, he talks about how pesticides are not broken down and eliminated from the body and stored in the fatty tissue (the brain is 60% fat). Many suffering from neurological diseases might have high levels of pesticides in their fatty tissue. The fatty tissue releases chemicals and toxins during a dietary fasting. These toxins are then broken down by the liver and excreted by the kidneys. The liver is the key organ to get rid of toxins through the bile. It seems hyperhidrosis sufferers are detoxifying themselves every day, through excess sweating.

Results

Toxic Encephalopathy. Toxic encephalopathy is a degenerative neurological disorder caused by exposure to toxic substances. It can be an acute or a chronic disorder. Exposure to toxic substances can lead to a variety of symptoms, characterized by an altered metal status. Encephalopathy is a general term describing brain malfunction. The most prominent characteristic of toxic encephalopathy is an altered metal status. Toxic encephalopathy has a wide variety of symptoms, which include memory loss, small personality changes, increased irritability, and insidious onset of concentration difficulties, involuntary movements, fatigue, seizures, arm strength problems and depression. MRI analyses have also demonstrated increased rates of dopamine synthesis in the putamen, reduced anterior and total corpus callosum volume, demyelization in the parietal white matter, basal ganglia, and thalamus, as well as atypical activation of frontal areas of the brain due to neural compensation, stated in Wikki links.

In the publication of, "a review of arsenic poisoning and its effects on human health," Dr. Saha and team found arsenic symptoms of chronic encephalopathy include persistent headache, diminished recent memory, distractibility, abnormal irritability, restless sleep, loss of libido, increased urinary urgency, and increased effects of small amount of ethanol. Secondary depression, anxiety, panic attacks and somatizations are common, in addition to the organic cognitive impairment documented by neuropsychological testing.

Lead. Elevated lead levels act on the HPA axis. Lead disrupts cognition through effects on the mesocorticolimbic dopamine pathway. Stress hormones act on this same pathway via the HPA axis. Maternal lead exposure can permanently alter basal corticosterone levels, stress responsively (example, permanent modification of HPA axis function) and brain catecholamines in offspring of both genders. Altered HPA axis function may serve a mechanism for the behavioral and catecholaminergic neurotoxicity associated with lead (12).

Arsenic Published in the Mayo Medical Laboratories, arsenic in blood, it states arsenic (As) exists in a number of toxic and nontoxic forms. The toxic forms are the inorganic species As (V), the more toxic As (III), and their partially detoxified metabolites, monomethylarsine (MMA) and dimethylarsine (DMA). Detoxification occurs in the liver as As (III) is oxidized to As (V) and then methylated to MMA and DMA. As a result of these detoxification steps, As (III) and As (V) are found in the urine shortly after ingestion, whereas MMA and DMA are the species that predominate more than 24 hours after ingestion. Blood concentrations of arsenic are elevated for a short time after exposure, after which arsenic rapidly disappears into tissue because if its affinity for tissue proteins. The body treats arsenic like phosphate, incorporating it wherever phosphate would be incorporated. Arsenic disappears into the normal boy pool of phosphate and is excreted at the same rate as phosphate (excretion half-life of 12 days). The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of methylated metabolites is 20 to 30 hours. A wide range of signs and symptoms may be seen in acute arsenic poising including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolytic, seizures, and metal status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nauseas, epigastria pain, colic (abdominal pain), diarrhea, and paresthesias of the hands and feet can occur.

Published by the Agency for Toxic Substance and Disease, it stated both arsenate and arsenite are well absorbed by both the oral and inhalation routes. Once absorbed, arsenates are partially reduced to

arsenites, yielding a mixture of As (III) and As (V) in the blood. As (III) undergoes methylation primarily in the liver to form monomehtylarsonic acid (MMA) and dimethylarsinic acid (DMA. The rate and relative proportion of methylation production varies among species. Most inorganic arsenic is promptly excreted in the urine as a mixture of As (III), As (V), MMA and DMA, Smaller amounts are excreted in feces. In most species, including humans, ingested organic arsenical compounds such as MMA and DMA, undergo limited metabolism, do not readily enter the cell, and are primarily excreted unchanged in the urine.

Arsenic trioxide (AsT) content, and monoamine levels in the central cortex, hippocampus, hypothalamus and corpus striatum were determined in mice administered AsT (3 and 10 mg/kg) for 14 days. The vertical and horizontal motor activity was also examined. The AsT content in discrete brain areas differed but was clearly close dependent. Metabolites and norepinephrine and dopamine increased in the cerebral cortex, hippocampus and hypothalamus and decreased in the corpus striatum in AsT treated mice. Metabolites of 5-hydroxytrypyamine increased in all the discrete brain areas. The vertical and horizontal motor activity was increased by AsT at mg/kg and decreased by AsT at 10 mg/kg. These results show that AsT modifies CNS metabolism and function as **low doses**. AsT penetrates the blood brain barrier to cause these effects (8).

Arsenic trioxide is readily absorbed by the digestive. Elimination is rapid at first but a certain amount is incorporated into the bones, muscles, skin, hair and nails (all tissue rich in Keratin) and eliminated over a period of weeks and months. Myoepithelial Cells of sweat glands contain Keratin.

Sodium arsenite treatment resulted in: decreased paired testicular weights, epididymaol sperm count, plasma LH, FSH, testosterone and testicular testosterone concentrations, and increased plasma concentrations of corticosterone. Testicular enzymes such as delta 5, 3 beta-HSD, 17 beta-HSD, and sorbitol dehydrogenase (SDH) were significantly decreased, but those of acid phosphatase (ALP), and lactate dehydrogenase (LDH) were significantly increased. A decrease in dopamine or an increase in noradrenaline and 5-HT in hypothalamus and pituitary were also noted after arsenic exposure. Arsenic causes testicular toxicity by germ cell degeneration and inhibits androgen production in adult male rats probably by affecting pituitary gonadotropins. Estradiol treatment has been associated with similar effects on pituitary testicular axis supporting the hypothesis that arsenite might somehow act through an estrogenic mode of action (9).

Mice exposed to high doses of As have found alteration in locomotor activity, brain neurochemistry, behavioral tasks, and oxidative stress. Male mice presented hyperactivity in group exposed to 0.5 mg of As/L and hyperactivity in group exposed to 50 mg As/L after 4 months of As exposure, whereas female mile exposed to .05, .5 and 5.0 mg As/L exhibited hyperactivity in every monthly test during As exposure. Furthermore, striatal and hypothalamic dopamine content was decreased only in female mice. Also decreases in tyrosine hydroxylase (TH) and cytosolic thioredoxin (Trx-1) mRNA expression in striatum and nucleus accumbens were observed in male and female mice. These results indicate that chronic As exposure leads to gender dependent alteration in dopaminergic markers and spontaneous locomotor activity, and down regulation of the antioxidant capacity of the brain (10).

Mouse offspring exposed to 50 parts per billion arsenic during the prenatal period had significantly elevated serum cortiocosterone levels, reduced whole hippocampus cortocotrophin releasing factor releasing, protein level and elevated dorsal hippocampus serotonin 5HT1a receptor binding and receptor-effectors coupling 5Ht1a receptor binding and receptor effectors coupling were not different in the ventral hippocampus formation, endocrinal or parietal cortices, or inferior colliculus. Prenatal arsenic exposure also significantly increased learned helplessness and measures of immobility in a forced swim task. These results suggest prenatal arsenic exposure may disrupt the regulatory interaction between the HPA axis and the serotonergic systems in the dorsal hippocampus formation in a manner that predisposes affected offspring to depressive like behavior. These results are the first to demonstrate that relatively low levels of arsenic exposure during development can have long lasting adverse effects on behavior and neurobiological markers associated with these behavioral changes. Prenatal arsenic exposure increases the sensitivity of dorsal hippocampus 5HT1a receptors to serotonin without altering the total number of receptors present (11).

While many chemical elements are essential for life, arsenic, cadmium, lead, and mercury have no known beneficial effect in humans. On the contrary, all four elements are confirmed or probable carcinogens, and they exhibit wide ranging toxic effects on many bodily systems, including nervous, endocrine, renal, immunological, and cardiovascular systems. Although signs and symptoms of chronic disease are consistent with effects of arsenic, cadmium, lead, and or mercury, physicians commonly have a

low index of clinical suspicion, and therefore levels of toxic elements are seldom investigated. Diagnosis may be challenging because multiple chemicals may contribute to subtle effects in chronic illnesses of any individual, and the effects may be synergistic. Interaction profiles complied by the US agency of Toxic Substances and Disease Registry report that renal toxicities of mixtures of lead plus mercury are greater than would be predicted knowing the toxicity does response of the individual elements. Similarly, neurological toxicities of mixtures of lead plus arsenic, lead plus methyl mercury, and lead plus cadmium are supra-additive. (13).

Arsenic exposure induces overproduction of reactive nitrogen species (RNS) and reactive oxygen species (ROS). Research demonstrated that exposure to arsenic results in impaired learning and concentration for studying, and deteriorated pattern memory and attention deficits in humans. It has shown in animal experiments that arsenic could pass through the blood brain barrier and invade the brain parenchyma (20).

According to Dr. Kaslow, on his website, he states arsenic effects are multiple and complex in terms of biochemistry. The mitochondria of cells accumulate the element. The private dehydrogenase complex (catalyzed formation of acetyl coenzyme A from the mitochondrial pyretic acid) is inhibited by As+++. Pyruvic acidosis may result; citric acid cycle function and formation of ATP are slowed. The citric acid cycle itself is impaired at the alpha ketoglutaric acid dehydrogenase step; formation of succinyl coenyme A is impaired. Both of these enzymatic steps require the active thiol, lipoid acid, Arsenic readily combines with sulfhydryl groups. Depending upon transport in various tissues, arsenic may react with any of the enzymes in the body that have sulfhydryl groups. 70% of commercial chickens raised for meat in the US are fed Roxarsone, a benzene arsenic compound. Arsenic must be methylated using methyl donors such as SAMe, trimethylglycine, dimethylglycine, and methionine. Some arsenic is bond to sulfur groups such as glutathione and excreted in the urine or bile. **He does not believe in giving NAC, although it will readily combine with arsenic, it will also move it around the body tissue and will not necessarily clear it from the body** (maybe this is why I developed paranoid thoughts when I took NAC).

Arsenic (III) methyltransferase (AS3MT). Published in Environmental research by Dr. Gonsebatt and team, they discovered human exposure to inorganic arsenic (iAs) has been associated with cancer and serious injury to various internal organs, as well as peripheral neuropathy, endocrine disruption, and diverse effects in the central nervous system. Using rodent models, it is possible to demonstrated arsenic accumulation in the brain that leads to defects in operant learning, behavioral changes, and affect pituitary gonadotrophins, iAs biomethylation in the central nervous system is a significant process, yielding products that are more reactive and toxic than the parent compounds. Mice received 2.5, 5, and 10 mg/kg/day sodium arsenite orally for 9 days. They investigated the distribution of iAs and its metabolites as well as the mRNA and protein expression of arsenic (III) methyltransferase (AS3MT), which encodes the key enzyme in iAs metabolism, in the cerebral cortex, hippocampus, striatum, mescencephalon, thalamus, cerebellum, hypothalamus, pons, medulla oblongata, and pituitary of mouse brain. The findings show that methylated arsenic metabolites are present in all brain regions studied suggesting that AS3MT is ubiquitously expressed in the brain and it is not inducible by dose of arsenite. There is also a dose related accumulation of arsenic species in all brain regions, with the highest accumulation observed in the pituitary. The higher distribution of arsenicals in pituitary can help to explain the neuroendrocine effects associated with iAs exposure (1).

In the rodent model that arsenic accumulates in the brain and result in operant learning, behavioral changes and damage to hypothalamic-pituitary-adrenal axis. AS3MT, a 43-kDa cytosolic protein, is a key enzyme in iAs metabolism. In the presence of cellular reductants such as thioredoxin (Txn1) or glutathione (GSH), AS3MT catalyzes the transfer of methyl group, using S-adenoyl-L-methionine (SAMe) as the methyl donor, to trivalent arsenicals, producing methylated and dim ethylated arsenicals. Impairing the expression of AS3MT reduces the ability of cells to methylate iAs. The biomethylation of iAs in the central nervous system is a significant process because it yields intermediate and final products that are more reactive and toxic that the parent compound this process also requires SAMe, Txn1, and GSH. The presence of methylated metabolites methylaronic acid (MMA) and dimethylarsenic acid (DMA) in mouse brain after arsenite exposure (1).

The pituitary is **not** protected by the blood brain barrier and receives its blood supply from the hypothalamic hyperphysical portal system, which could explain the larger accumulation of arsenic in this region. The pituitary is also a key regulator of neuroendocrine balance and is under strict control of the hypothalamus since the hypothalamic releasing factors regulate the release of the anterior pituitary trophic hormones. The high accumulation of arsenic in the pituitary and hypothalamus could explain the damage

to the HPA axis observed when mice received arsenic. Adenocorticotropic (ACTH) hormone levels were significantly higher the ACTH controls, dopamine and **norepinephrine levels** were shown to significantly change in the hypothalamus and pituitary in mice and rats that ingested arsenic. Inorganic arsenic exposure alters cholinergic, glutamateragic and monoaminergic systems in the rodents. AS3MT is a SAMe dependent enzyme that requires Trx1 and GSH as cellular reductants. In the CNS SAMe is also the methyl donor for the catechol O-Methytransferase (COMT), a key enzyme in the biotransformation of endogenous catecholamine neurotransmitters, such as norepinephrine and cateholestrogens. The pituitary appears to be the most affected at both the does and exposure duration tested. Endocrine system disorder is likely to be an important component of toxic effects associated to iAs exposure (1).

Published by the UPMC Brain Surgery Website, What is the Pituitary Gland, it states the pituitary gland is a pea sized gland located at the base of the skull between the optic nerves. The pituitary gland secretes hormones. The pituitary is sometimes referred to the master gland as it control hormones functions such as our temperature, testosterone production in males and ovulation and estrogen production in females. In effect the gland functions as our thermostat that controls all other glands that are responsible for hormone secretion. The gland is a critical part of our ability to respond to the environment most often without our knowledge. The pituitary gland actually functions as two separate compartments an anterior portions (adenohypohysis-hormone producing) and the posterior gland (neurohypophysis). The anterior gland actually is made of separate collection of individual cells that act as functional units (it is useful to consider them as individual factories) that are dedicated to produce a specific regulatory hormone messenger or factor. These factors are secreted in response to the outside environment and the internal bodily responses to this environment. These pituitary factors then travel through a rich blood network into the blood stream and eventually reach their specific target gland. They then stimulate the target gland to produce the appropriate type and amount of hormone so the body can respond to the environment correctly. Similar to the Cortisol factory are the growth hormone, prolactin, gonadotropin, and thyroid. These five axies (factories) function as the anterior pituitary gland neuroendocrine unit. If any one of these factories become excited and start to overproduce their respective hormone factor the net result is excess production of the final hormone product. So in the above example, if the Cortisol cells (corticotrophs) lose their ability to respond to the normal stimuli from the environment and hypothalamus develop their own independent, uncontrolled autonomous secretion they will produce more Cortisol than the body requires. In return the adrenal gland will be over stimulated and secrete unregulated and unneeded catecholamine (stress chemicals).

Pituitary tumors are often misdiagnosed because of the confusing array of symptoms they present. Conditions such as osteoporosis, sexual dysfunction, depression and infertility, or growth disorders can be the result of abnormalities in the pituitary or master gland. Aspartic acid is an amino acid occurring in the pituitary gland, hypothalamus and testes.

The HPA axis is a major part of the neuroendocrine system that controls reaction to stress and regulates many body process, including digestion, the immune system, mood and emotions, sexuality, and energy and storage.

Published in International Journal of Molecular Sciences, individual variations in inorganic arsenic metabolism may influence the toxic effects. AS3MT can catalyze the transfer of methyl group from S-adenosyl-I-methionine to trivalent arsenical, may play a role in arsenic metabolism in humans. Since the genetic polymorphisms of AS3MT gene may be associated with the susceptibility to inorganic arsenic toxicity, relationships of several single nucleotide polymorphisms (SNPs) in AS3MT with inorganic arsenic metabolism have been investigated. Results of genotype dependent differences in arsenic metabolism for most SNP's in AS3MT were inconsistent throughout the studies. Nevertheless, two SNP's, AS3MT 12390 (rs3740393) and 14458 (rs11191439) were consistently related to arsenic methylation regardless of the populations examined for the analysis. Thus, these SNP's may be useful indicators to predict the arsenic metabolism via methylation pathways (2).

Arsenic occurs as monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) in humans, and the methylation pattern demonstrates **large interindividual differences**. The fraction of urinary MMA is a marker for susceptibility to arsenic related diseases. Several studies have shown an association between an increased fraction of MMA in urine, probably reflecting the highly toxic MMA III in tissues, and an increased risk of various related adverse health effects. Arsenic is metabolized by a series of reduction and methylation reactions, S-Adenosyl methionine (SAM) is the main methyl donor, implying that arsenic methylation is dependent on factors influencing one carbon metabolism. Methyltransferase genes are AS3MT, DNA-methyltransterase 1a and 3b (DNMT1a and DNMT3b), phosphatidylethanolamine N-

methyltransferase (PEMT) and betaine-homocysteine methyltransferase (BHMT). Polymorphisms in AS3MT significantly predicted arsenic metabolism across different populations, suggesting that AS3MT may have an impact on arsenic metabolite patterns in populations worldwide (15).

Methylenetetrahydrofolate Reductase (MTHFR). MTHFR is an enzyme in humans encoded by the MTHFR gene. Methyleneetetrahydroflolate reductase catalyzes the conversion of 5, 10 methylenetetrahydroflolate to 5-methyltetrahydrofolate, a co substrate for homeocysteine methylation to methionine. 5-Methyltetrahydroflolate is used to convert homecysteine (a potentially toxic amino acid) to methionine by the enzyme methionine synthesis. MTHFR activity may be inhibited by binding of dihydrofolate (DHF) and S-adenosylmethionine (SAM or AdoMet). MTHFR can also be phosphorylated-this decreases its activity by 20% and allows it to be more easily inhibited by SAM. MTHFR is located on chromosome 1 location p36.3 in humans. There are DNA sequence variants, the two most investigated are C677T (rs1801133) and A1298C (rs1801131) single nucleotide polymorphisms (SNP).

Published in Toxicology and Applied Pharmacology, Dr. Chen and team found inter individual variability in arsenic metabolism capacity may also contribute to variation in susceptibility to the effect of arsenic. 1 Glutathione S-transferase (GSTO1) and MTHFR are enzymes involved in arsenic metabolism pathways. In a case control study of 594 skin lesion cases and 1041 controls, the does response relationship of skin lesion risk with urinary monomehtylarsonous acid percentage was more apparent that those with other methylation indices. **Individuals with the MTHFR 677TT/1298AA** and 677CT/1298AA diplotypes were 1.66 and 1.77 times more likely to have skin lesions, compared with those carrying 677CC/1298CC diplotype. Arsenic induced health effects may be especially deleterious in subsets of the population carrying susceptible variants of genes relevant to arsenic metabolism. The skin lesion in the study population attributable to the MTHFR 677TT/1298AA and 677CT/1298AA diplotypes was estimated to be 7.5%. The corresponding estimated attributable proportion for the GSTO1 at risk diplotype was 8.9% (4).

Mutation of the MTHFR gene have been shown to be associated with a predisposition to developing diabetic nephropathy in specific populations. Two MTHFR mutations in human MTHFR gene A1298C and C677T, whose association with diabetic nephropathy is already known, was determined in an Israeli Jewish population with type 2 diabetes mellitus. Both A1298C and C677T are highly prevalent in the diabetic population (17).

Genetic polymorphisms. Arsenic induced diseases differs greatly between individuals, possibility due to interindividual variations in As metabolism that affect retention and distribution of toxic metabolites. They studied how polymorphisms in six gene affected the urinary metabolite pattern in a group of women who were exposed to approximately 200 (micro)g/L As in drinking water. These women had low urinary percentages of monomethylated As (MMA) and high percentage of dim ethylated As (DMA). MMA has been associated with adverse health effects and DMA has the lowest body retention of the metabolites. The genes studied were AS3MT, glutathione S-transferase omega 1 (GSTO1), 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), MTHFR, and glutathione S-transferases mu 1 (GSTM1) and theta 1 (GSTT1). They found three intronic polymorphisms in AS3MT (G12390C, C14215T, and G35991A) associated with a lower percentage of MMA (%MMA) and a higher percentage of DMA (%DMA) in urine. The variant homozygotes showed approximately half the %MMA compared with wild type homozygotes. These polymorphisms were in strong linkage, with high allelic frequencies (72-76%) compared with other populations. We also saw minor effects of other polymorphisms in the multivariate regression analysis with effect modification for the deletion genotypes for GSTM1 (affecting %MMA) and GSTT1 (affecting % MMA and %DMA). For pregnant women, effect modification was seen for the folate-metabolizing genes MTR and MTHFR. In conclusion, these findings indicate that polymorphisms in AS3MT and possibly GSTM1, GSTT1, MTR and MTHFR are responsible for a large part the interindividual variation in As metabolism and susceptibility. Studies have shown that the trivalent forms, particularly monomethylarsonous acid (MMAIII) are generally more toxic than the pentavalent forms. Thus the large variability in the distribution of metabolites in urine among individuals and population groups might be associated with differences in tissue distribution and retention of toxic metabolites. This, in turn, is likely to lead to variation in susceptibility. A number of studies indicate that increased percentage of MMA (%MMA) and decreased percentage of DMA (%DMA) in urine are associated with an increased in As retention in the body. Hereditary differences in As metabolism are very likely due to the variation. S-Adenosyl-methionine (SAM) is the methyl donor for methylation of As, and polymorphisms in genes involved in SAM metabolism (example, one-carbon metabolism), for example, MTHFR and MTR, may affect As metabolism (5).

AS3MT can catalyze the transfer of a methyl group from S-adenosyl-I-methionine (SAM or AdoMet) to trivalent arsenical, may play a role in arsenic metabolism in humans. Since the genetic polymorphisms of AS3MT gene many be associated with the susceptibility to inorganic arsenic toxicity, relationships of several single mucleotide polymorphisms (SNP's) in AS3MT with inorganic metabolism have been investigated. Results of genotype dependent differences in arsenic metabolism for most of SNP's in AS3MT were inconsistent throughout the studies. Nevertheless, two SNP's, AS3MT 12390 (rs3740393) and 14458 (rs11191439) were consistently related to arsenic methylation regardless of the populations examined for the analysis. Thus, these SNP's may be useful indicators to predict the arsenic metabolism via methylation pathways (6).

Human AS3MT is known to catalyze the methylation of arsenite. A single nucleotide polymorphism (SNPs; rs17885947, M287T (T860C)) in AS3MT gene was shown to be related to enzyme activity and considered to be related to genetic susceptibility to arsenic (16).

Individual variability in human arsenic metabolism has been reported frequently, this variability could be the underlying determinant of individual susceptibility to arsenic induced diseases in humans. Metabolic profiles suggests that genetic factors could underlie interindividual variation in arsenic metabolism. Two genes responsible for arsenic metabolism, human purine nucleoside phosphorylase (hNP), which functions as an arsenate reductase converting arsenate to arsenite, and human glutathione S-transferase omega 1-1 (hGSTO-1-1), which functions as a monomethylarsonic acid (MMA) reductase, converting MMA(V) to MMA (III) (18).

Reactive Oxgenative Species (ROS) and Cellular Antioxidants. ROS can be toxic to cells and are chemically reactive molecules containing oxygen. ROS form as a natural by-product of the normal metabolism of oxygen and have important roles in cell signaling. ROS can be beneficial as they are used by the immune system as a way to attack and kill pathogens. ROS can be highly reactive and thereby able to damage all macromolecules, including lipids, proteins and nucleic acid. One of the best know toxic effects of oxygen radical is damage to cellular membranes, which is initiated by a process known as lipid peroxidation. A common target for peroxidation is unsaturated fatty acid resent in membrane phospholipids. Sequential reduction of molecular oxygen lead to formation of a group of ROS, such as H2O2, super oxide anion and hydroxyl radical. Many neurodegenerative conditions are now thought to be caused by toxic chemicals called free radicals that can damage nerve membranes and other vital parts of the brain. Excess formation of free radicals can arise either from an overproduction of these chemicals or from a relative lack of other chemicals called antioxidants that neutralize free radical action. The Department of Neurology and Brain Institute, University of Florida, found free radical mediated mechanisms contribute to the development of several neurodegenerative disease. They found increase activity of the cellular antioxidant enzyme superoxide dismutase (SOD) could potentially disrupt a balance in oxidative metabolism, since enhanced H2O2 production without compensatory changes in catalase or glutathione peroxidase may lead to increased production of more potent free radicals such as the hydroxyl radical. N-Acetylcysteine (NAC) a sulfhydryl amino acid has several characteristics promoting its usage as an antioxidant, including scavenging of the hydroxyl radical, increased synthesis of reduced glutathione peroxidase and diminished production of H2O2 (I talk more about prescription strength oral NAC, in the treatments section and how it briefly helped). During times of environmental stress (UV or heat exposure) ROS levels can increase dramatically causing damage to cell structure resulting in oxidative stress. Oxidative stress represents an imbalance between the production of ROS and a biological systems ability to readily detoxify the reactive intermediates or to repair the resulting damage. Cells are normally able to defend themselves against ROS damage with cellular enzymes such as SOD, CAT and GSH-px. In the European Society of Intensive Care Medicine, the authors discuss how ROS is implicated in the pathogenesis of hypoxia-reoxygenation injury. The authors found that N-acetylcysteine abolished the increased H2O2 concentration and oxidized glutathione levels and tended to reduce glutathione ratio and lipid H2O2 levels in the cerebral cortex. N-acetylcysteine at 100 mg/kg/h also increased the cerebral extra cellular taurine levels (29).

Chaudhary and team found Arsenic is a well-known heavy metal that causes tissues damage, including immune system. Arsenic is an uncoupler of mitochondrial oxidative phosphorylation that induces generation of ROS. Various studies have reported that arsenic is immuntoxic. Arsenic metal interferes with the heme synthesis path way (the heme metabolic path way is highly susceptible to alteration induced by metal ions) that inhibits the aminolevulinic acid dehydrates enzyme (is a second enzyme in the **porphyria** heme pathway and converts delta-aminolevulinic acid to porphobilinogen) and these enzymes are responsible for the synthesis of heme. Due to decrease of the ALAD enzyme activity, the heme

synthesis path way is inhibited. The principal biochemical mechanism in acute arsenic intoxication is the reversible combination of arsenic with susceptible sulfhydryl-containing enzymes. Oxidative stress has also been identified as an important mechanism of arsenic toxicity. Arsenic induces oxidative DNA damage and increased lipid per oxidation due to excessive generation of free radicals. Various reports the inorganic arsenic inhibits several of the antioxidant systems in the body, such as glutathione, glutathione peroxidase, thioredoxin reductase, total thiol and SOD. Also caused a significant increase in MDA levels, IL-6 and TNF-alpha (14).

One of the few scientist performing critical research in the area of hyperhidrosis is Dr. Karaca (45) and he found that tempol, a SOD mimetic, increase the half-life of nitric oxide and results in vasodilatation, hypotension, and reflex activation of sympathetic nervous system. Reactive oxygen species (ROS) may directly activate both central and peripheral sympathic nervous system activity. Increased ROS production caused oxidative damage in hyperhidrosis patients compared to healthy subjects, where cellular antioxidant enzymes such as superoxide dismutase (SOD), Malondialdehyde (MDA) where significantly higher than controls. He also found catalase (CAT) and glutathione peroxidase (GSH-px) where significantly lower in hyperhidrosis patients compared to controls. On the internet it stated that CAT and GSH-px both help in the decomposition of hydrogen peroxide to water and oxygen. The CAT enzyme can covert 40 million molecules of hydrogen peroxide to water and oxygen each second. CAT has the ability to react with H2O2 because of its basic make-up. It is composed of four polypeptide chains of amino acids, which are then strung, together to create four porphyrin groups. PH plays an important factor in how CAT reacts with H2O2 in the body. Human CAT functions properly at 7, with a fairly broad range in which the reaction will not change, ranging from 6.8, all the way up to 7.5 (I believe that low levels of CAT and GSH-px are exhausted or over extended trying to process an extraordinary amount of hydrogen peroxide. It is similar to a marathon runner running two marathons in one day).

In another article by Dr. Karaca (46) he found the expression of endothelial nitric oxide synthase (eNOS) in eccrine clear cells, he has suggested that nitric oxide (NO) many play a role in the physiology of production and/or excretion of sweat in the human skin eccrine gland. He found plasma NO levels were found to be significantly increased in hyperhidrosis patients compared to healthy subjects. NO is an important messenger molecule in the brain, playing an important role in learning and memory, in particular via the ERK/CREB signaling pathway. NO is also a neurprotective agent; multiple mechanism having demonstrated that can contribute to cell survival as level of antioxidants and trophic factors are reduced with aging according to Thatcher (47). According to Wultsch (11) mice lacking the neuronal isoform of nitric oxide synthase (NOS-I) display a characteristic behavioral profile consisting of reduced anxiety and impaired learning and memory, paralleled by differential expression of the glucocorticoid receptor and GABAergic genes. Lee (48) and his team found the formation of reactive oxygen and nitrogen species is a precipitating event in an array of neuropathlogical conditions. Dr. Patel and team found NO, physical exercise and or/antidepressant drugs, through the increased release of norepinephrine and BDNF, have been shown to exert profound protective, pro-survival effects on neurons otherwise compromised by injury, disease, prolonged stress and subsequent depression iv vivo (49). Dr. Ferreira and team found NO is an atypical neurotransmitter that has been related to the path physiology of major depression. Increased plasma NO levels have been reported in depressed and suicidal patients. Inhibition of neuronal Nitric Oxide Synthase (nNOS), on the other hand, induces antidepressant effects in clinical and preclinical trails. A preferential nNOS inhibitor 7-nitroindazole (7-NI) changed the expression of genes related to transcription in the CREB pathway (30).

In response to excessive ROS levels, transcriptionally-dependent mechanisms drive the up regulation of ROS scavenging proteins which, in turn, limit the extent of brain damage. In repressed CREB mice scientist found there was a dramatic increase in tyrosine nitration (a marker of ROS formation). They examine the contribution of the CREB/CRE pathway to neuroprotection and its potential role in limiting ROS toxicity. They found CREB functions as a pivotal upstream integrator of neuroprotective signaling against ROS mediated cell death. Canadian scientist found cellular and molecular changes in the hippocampus of rats subjected to repeated restraint stress had suppressed hippocampal cell proliferation, decreased brain derived neurotrophic factor (BDNF) and increased levels of SOD (50). Sarandol found with patients with major depressive disorder MDA and SOD levels were significantly higher than control subjects (51). Ethanol was one of few drugs to have a positive effect on my hyperhidrosis, but it also increased the symptoms of my insomnia significantly. Scientist found ethanol increase MDA formation and SOD, CAT and GSH-px were reduced by ethanol (NAC improved my insomnia briefly, alcohol increased insomnia ????)(31).

Unlike the mature animal, immature mice transgenic for copper/zinc superoxide dismutase (SOD1) have greater brain injury after hypoxia-ischemia than their wild type nontransgenic littermates. To assess the role of oxidative stress in the pathogenesis of this injury, we measured histopathological damage, lipid per oxidation products, enzymatic activities of catalase and glutathione peroxidase, and H2O2 concentration in these animals before and after hypoxic ischemic injury. Lipid per oxidation products were significantly increased 2 hours after the insult in both transgenic and nontransgenic brains in hippocampus, the most damaged brain region. Catalase activity did not increase in response to SOD1 over expression or injury in either group. However, glutathione peroxidase activity, unchanged in response to over expression, decreased significantly 24 hours after injury in both groups. At 24 hours after injury, greater H2O2 accumulation was observed in transgenic brains. Because SOD1 dismutates superoxide to H2O2, overexpression of SOD1 in the presence of developmentally low activities of the catalytic enzymes glutathione peroxidase and catalase leads to an increased production of H2O2, and may explain the increased brain injury observed after hypoxia ischemia in neonatal SOD1 mice (32).

Dr. McCord and the University of Colorado, Denver, published online August 6, 2008, found that SOD production increases in a wide variety of pathological states, especially those involving inflammation or ischemic injury. Most of the literature has described systems wherein added or over expressed SOD produced beneficial effects, yet in some circumstances SOD provided no benefit, or was clearly detrimental, exacerbating cell injury or death. He proposes that the mechanisms underlying the hormesis are related to the paradoxical abilities of the super oxide radical to serve as both an initiator and a terminator of the free radical mediated chain reaction that results in lipid per oxidation. Lipid per oxidation is a universal feature of oxidative stress, causing loss of cellular structure and function. Under any given condition, the optimal concentration of SOD is that which decreases chain initiation without elimination of the chain termination properties of the radical, resulting in a minimum of net lipid per oxidation. Superoxide is not, as first thought, just a toxic but unavoidable byproduct of oxygen metabolism. Rather, we now appreciate that it is a carefully regulated metabolite capable of signaling and communicating important information to the cell's genetic machinery. In a healthy cell, the super oxide produced is detoxified by the antioxidant SOD, which catalyzes the reaction: O2+O2+2H> H2O2+O2. SOD and CAT normally detoxify the radical if super oxide concentration rises too high, oxidation of proteins, lipids, and DNA occur and various signaling pathways may be triggered. SOD can be damaging when SOD produces H2O2 as a product, more SOD would produce more H2O2, which is toxic to cells. SOD will dramatically lower the steady state concentration of super oxide, but cannot alter the steady state rate of its conversion to H2O2, as this is limited by the rate of super oxide production. It has also been suggested numerous times that the toxicity of high dose SOD might be due to a weak peroxide activity of Cu, Zn-SOD. SOD displays bell shaped dose response curve if that system involves lipid per oxidation. This convinces us that super oxide radical can act both as initiator of lipid per oxidation and terminator of lipid per oxidation. This realization provides a rational basis for the bell shaped dose response curves observed for SOD in systems involving lipid peroxidation, and argues that, for any specific set of conditions, there is a single, optimally protective concentration of SOD. It underscores the importance of balance between oxidants and antioxidants. An exciting approach to the therapeutic use of exogenous SODs is the controlled induction of the family of antioxidant enzyme regulated directly or indirectly by the Antioxidant Response Element (ARE). The ARE is a promoter element activated by the transcription factor NrF2 (Nuclear factor like 2)(NrF2 has been shown to interact with CREB). A number of phytochemicals long known to traditional medicine appear to be a safe and effective means of up regulating these enzymes in humans via NrF2 dependent mechanisms. ARE are largely coordinately regulated, directly or secondarily, by ARE regulated promoters. It may be highly artificial to manipulate the concentration of SOD alone, observing effects on net lipid per oxidation, when in vivo the entire network or antioxidant enzymes would more likely be induced in concert. This means glutathione levels would be raised via increased synthesis, glutathione reductase and peroxides would be induced to eliminate lipid hydro peroxides, and various peroxiredoxins would also be induced. All of these actions would serve to limit lipid per oxidation. Hence, an animal's natural response to oxidative stress might be much less likely to produce hormetic effects than laboratory experiments that manipulate any single antioxidant enzyme such as SOD.

Published in the Journal of Neurochemistry, 2009 March; 108(5): 1251-1264, Lee and team found formation of reactive and nitrogen species is a precipitating event in an array of neuropath logical conditions. In response to excessive ROS levels, transcriptionally-dependent mechanisms drive the up regulation of ROS scavenging proteins which, in turn, limit the extent of brain damage. Here, we

employed a transgenic approach in which CREB-mediated transcription is repressed (via A-CREB) to examine the contribution of the CREB/CRE pathway to neuroprotection and its potential role in limiting ROS toxicity. Using the pilocarpine-evoked repetitive seizure model, we detected a marked enhancement of cell death in A-CREB transgenic mice. Paralleling this, there was a dramatic increase in tyrosine nitration (a marker of reactive species formation) in A-CREB transgenic mice. In addition, inducible expression of PGC1-alpha (peroxisomes proliferator-activated receptor gamma co activator-1 alpha) was diminished in A-CREB transgenic mice, as was activity of complex of the mitochondrial electron transport chain. Finally, the neuroprotective effect of BDNF against ROS medicated cell death was abrogated by disruption of CREB-mediated transcription. Together, these data both extend our understanding of CREB functionality and provide in vivo validation for a model in which CREB functions as a pivotal upstream integrator of neuroprotective signaling against ROS mediated cell death. CREB plays a role in the regulation of ROS detoxification. For example, several studies have shown that CREB is a direct regulator of antioxidant gene expression and induces the expression of PGC-1 alpha, a key effector of ROS detoxifying enzyme expression and mitochondrial biogenesis. These findings raise the interesting prospect that CREB forms the central molecular building block of the cellular ROS defense mechanism. As an important validation of the functional role of CREB in protection against oxidative stress, transient transfection of a constitutively active form of CREB conferred significant protection against H2O2 mediated cell death. Although much of the work examining CREB and neuroprotection has focused on its regulation of neurotrophins and ant apoptotic genes, the data presented here indicate that CREB also stimulates a potentially neuroprotective preconditioning response as well. Along these lines, our cell culture date revealed that pretreatment with BDNF conferred protection against H2O2 mediated cell death via a CREB dependent mechanism. Furthermore, the in vivo neuroprotective effects of BDNF were dependent on CREB and were correlated with a decrease in oxidative load. A-CREB transgenic mice, SE-evoked PGC-1 alpha expression was blunted, indicating a critical upstream role for CREB in inducible PGC-1 alpha expression. Given that PGC-1 alpha drives the expression of many ROS detoxifying enzymes, including GPx1 and SOD2, these data support a model wherein a CREB/PGC-1 alpha signaling cassette regulates oxidative stress. A disruption of CREB signaling may be a key event in disease dependent increase in oxidative load.

Hydrogen Peroxide (H2O2). ROS including H2O2 is a naturally produced in organisms as a byproduct of oxidative metabolism. External sources, such as cigarette smoke or excessive caloric intake may significantly increase endogenous oxidant load and shift the balance to an abnormally high level of ROS. Excessive production of ROS, such as H2O2, lead to oxidative stress and disease. H2O2 has the ability to harm microorganisms, it also has the ability to kill our body's cells. The damaging power comes from the transition to highly reactive hydroxyl radical that indiscriminately react with a wide variety or organic substrates causing peroxidation of lipids, cross linking and inactivation of proteins, and mutations in DNA. The body has tools to combat against oxidative stress and these enzymes are employed to rapidly dismutate H2O2 to water to prevent accumulation of toxic H2O2 levels. Those tools are cellular antioxidants such as SOD, CAT and GSH-px. Also, SOD is spontaneously converted to H2O2 which can freely pass through the membrane. However, abnormal low levels of GSH-px might allow H2O2 in cells to increase. Prescription strength NAC is used to eliminate H2O2 and reduce free radicals. During inflammation, H2O2 is produced by white blood cells as a first line of defense against mico-orgransims that have invaded the body. It has already been postulated that H2O2 is as important for cell functioning as other ubiquitous signaling molecules such as cAMP, NO and calcium. While these oxidants are important in protecting us from infection, they can cause oxidative damage during chronic inflammatory activity. Inflammatory process often overshoot in their reaction leading to excessive production of ROS, such as H2O2 (15). The overproduction of H2O2 might explain the substantial increase in my hyperhidrosis and insomnia, while I was infected with LD.

H2O2-dependent modification of the target proteins can cause their activation or inactivation. For instance, H2O2 down regulates transcription factors such as p53, Jun, and Fos, but leads to activation of NF-kappa B and c-Jun N-terminal kinase (JNK) pathways. An important group of molecules that are down regulated by H2O2 is the protein tyrosine phosphatase (PTP) group, evolutionarily conserved molecules that play a central role for transmitting signal from cell surface receptors to the nucleus. T cells responses are highly regulated by tyrosine phosphorylation. It is not astonishing that H2O2 affects T cell activity by balancing the activities of tyrosine kinases and phosphates. The activation of T cell receptor signal pathways seems to occur via inhibition of PTPs and to result in activation of all three members of the MAPK family: ERK, p38 and JNK. It is proposed that the oxidative activation of T cells not only occurs

during pathological conditions of chronic oxidative stress, but also regularly as a very early response of the immune system to an invading pathogen. It may be that T cells sense small quantities of ROS long before inflammatory stages are reached. Initially, the response of T cells to H2O2 was believed to be solely a response to its inflammatory environment, where activated macrophages and Neutrophils increase the local H2O2 concentrations. More recently, there is evidence that T cells themselves produce H2O2 upon stimulation of their antigen receptor. In conclusion, H2O2 produced in the body as a byproduct of oxidative metabolism, and most organisms have evolved powerful mechanisms to eliminate it. During inflammation, H2O2 is produced by white blood cells as a first line of defense against microorganisms that have invade the body. Inflammatory process often lead to excessive production of ROS, including H2O2 (33).

Stated on the internet, by Dr. Andrew Cross, from the Faculty Molecular and Experimental Medicine, Scripps Clinic and Research Foundation. H2O2 is made by quite a few enzymes in the body. In particular, some enzymes breaking down certain amino acids and fatty acids (D-amino acid oxidase and acyl-CoA oxidase) make significant amounts of H2O2. Since H2O2 can be damaging to normal tissue, these enzymes are kept inside specialized organelles inside cells called peroxisomes. The peroxisomes also contain large amounts of CAT to break down the H2O2 before it can escape. Other enzymes that make significant amounts of H2O2 are plasma amine oxidase and xanthine oxidase. In addition to enzymes that produce H2O2 as part of their normal catalytic cycle, many enzymes that undergo oxidation and reduction make H2O2 and other ROS by autoxidation (a kind of side reaction that is not part of their catalytic cycle). This happens quite a bit in the mitochondria. Many of these autoxidation reactions do not produce H2O2 directly, but rather super oxide (the product of adding one electron to an oxygen molecule). In order to get rid of super oxide (which is more toxic than H2O2) the body also contains lots of super oxide dismutase that converts the super oxide into water and H2O2. One of the most interesting sources of super oxide in the body is that produced by white blood cells when they encounter harmful microorganisms. The white blood cells produce very large amounts of super oxide, H2O2 and even hypochlorous acid to kill germs.

Peroxynitrite (ONOO) is an oxidant and nitrating agent because of its oxidizing properties, peroxynitrite can damage a wide array of molecules in cells, including DNA and proteins; ONOO inhibit the activation of CREB and is the reaction of H2O2 and nitrite. Pacher discuss that NO has emerged as a fundamental signaling device regulating virtually every critical cellular function, as well as a potent mediator of cellular damage in a wide range of conditions. Recent evidence indicates that most of the cytotoxicity attributed to NO is rather due to peroxynitrite, produced by the diffusion controlled reaction between NO and another free radical superoxide anion. Peroxynitrite interacts with lipids, DNA and proteins via direct oxidative reaction or via indirect radical mediated mechanisms. These reactions trigger cellular responses ranging from subtle modulations of cell signaling to overwhelming oxidative injury, committing cells to necrosis or apoptosis (34).

Peroxisomes contain enzymes that work by transferring hydrogen from a substrate to oxygen, there by producing H2O2 as a byproduct. H2O2 is toxic to cells, but peroxisomes also contain enzymes that is capable of converting H2O2 to water. Some functions of peroxisomes include detoxifying alcohol, bile acid formation using oxygen to break down fats.

Peroxisome proliferator activated receptor gamma coactivator 1-alpha (PGC-1alpha) regulates the genes involved in energy metabolism. This protein can interact with the activities of CREB and nuclear respiratory factors (NRF). It provides a direct link between external physiological stimuli and the regulation of mitochondrial biogenesis, and is a major factor that regulates muscle fiber type determination. This protein may be also involved in controlling blood pressure, regulation cellular cholesterol homoeostasis. PGC-1 alpha is known to be activated by a host of factors: including ROS and reactive nitrogen species (RNS). Bile acid receptor (BAR) also known as Farnesoidx Receptor (FXR) is expressed in high levels in the liver and intestine. FXR interacts with PGC1-alpha. Also, PGC-1 alpha is strongly induced by cold exposure, adaptive thermo genesis, mitochondrial biogenesis, glucose/fatty acid metabolism. PGC-1 expression is high in the brain and kidney, but low in the liver.

Published in Clin. Exp. Pharmacol. Physiol., 2009 Apr; 36(4):367-72. Equb 2008 Oct 15, entitled "Melatonin protects against hydrogen peroxide-induced gastric injury in rats." Dr. Mohamadin and team evaluate the potential protective effects of Melatonin (MT) against Hydrogen peroxide (H2O2) induced gastric lesion in rats. H2O2 induced gastric oxidative stress, as indicated by depletion of reduced glutathione (GSH), inhibition of glutathione peroxidase (Gpx) activity and elevation of malonedialdehyde (MDA) levels. These effects were accompanied by decreased gastric tissue levels of prostaglandin (PG) E

(2) and nitric oxide (NO), as well as increased levels of tumor levels of tumor necrosis factor (TNF)-alpha. The protective effects of MT were accompanied by significant inhibition of the H2O2 induced reduction in gastric content of GSH and Gpx activity and elevation in MDA levels. Furthermore, MT antagonized H2O2 induced reduction of gastric PGE (2) and NO levels and elevation of TNF-alpha. In conclusion, MT protects rat gastric mucosa against H2O2 induced damage. The observation protective effects of MT can be attributed, at least in part, to its antioxidant properties, preservation of PGE(2) and NO levels, as well as inhibition of TNF-alpha induction in gastric tissues. Melatonin made me sleepy for only a few hours and over a short period of time slightly reduced my sweating. Under stressful situation it was not effective.

In FEBS Letter, 2000, Dec. 1, 486(1): 10-13, entitled "Hydrogen peroxide in the human body" by Dr. Halliwell. His team found H2O2 is widely regarded as a catatonic agent whose levels must be minimized by the action of antioxidant defense enzymes. In fact H2O2 is poorly reactive in the absence of transition metal ions. Exposure of certain human tissues to H2O2 may be greater than is commonly supposed: substantial amounts of H2O2 can be present in beverages commonly drunk (especially instant coffee), in freshly voided human urine, and in exhaled air. Levels of H2O2 in the human body may be controlled not only by catabolism but also by excretion, and H2O2 could play a role in the regulation of renal function and as an antibacterial agent in the urine. Urinary H2O2 levels are influenced by diet, but under certain conditions might by a valuable biomarker of oxidative stress. It is therefore widely thought that H2O2 is very toxic in vivo and must be rapidly eliminated, employing enzymes such as catalases, glutathione Peroxidases and thioredoxin linked system. The danger of H2O2 largely comes from its ready conversion to the indiscriminately reactive hydroxyl radical, either by exposure to ultraviolet light or by interaction with a range of transition metal ions, of which the most important in vivo is probably iron. H2O2 is generated in vivo by the dismutation of super oxide radical, both non-enzymatic ally and catalyzed by super oxide dismutase enzymes. H2O2 is also directly produced by a range of oxidase enzymes including glycol late and monoamine oxidase as well as by the peroxisomal pathway for B-oxidation of fatty acids. With apparent exception of the cardiac muscle, mitochondria in most tissue appear to have limited capacity to remove H2O2, in that they readily generated substantial amounts of H2O2 in vitro and probably in vivo. Although mitochondria contain glutathione peroxidase and thioredoxin-linked peroxidase activities, the efficiency of these enzymes in removing H2O2 is uncertain given the ease with mitochondria release H2O2. Another possibility is that excretion of H2O2 represents a metabolic mechanism for controlling its levels in the human body. If so, measurement of urinary H2O2 levels may represent a valuable tool for assessment of oxidative stress, since H2O2 can be measured rapidly and simply. Some studies have claimed substantial levels of H2O2 in human plasma, but others have claimed levels to be very low, at or close to zero. The latter data seem more credible, since H2O2 added to human plasma disappears rapidly. In part, it is degraded by the traces of catalase present, but H2O2 can also react with heme proteins, ascorbate, and protein-SH groups. In vivo, H2O2 generated in plasma could also diffuse into erythrocytes, white cells, endothelial cells and platelets for metabolism. However, the studies in could be interpreted to suggest that H2O2 can be detected at high levels in plasma under assay conditions in which its removal is prevented. This implies that human plasma may be continuously generating H2O2. One enzyme involved in this process, at least under pathological conditions, appear to be xanthine oxidase. Levels of circulation and endothelium-bound xanthine oxidase are increased as a result of tissue injury. H2O2 appears to be a ubiquitous molecule. We exhale it, excrete it and take it in from diet. It can be detected in drinking water, rain water and sea water. The data emphasize the importance of metal ion sequestration in preventing the toxicity of H2O2 in vivo by decreasing the occurrence of Fenton chemistry, and help explain why a failure of such sequestration can produce devastating tissue damage in almost all organs of the body.

Stress. Hyperhidrosis should be classified as a stress disorder. Stress occurs in the human body because of a state of alarm and adrenal production. Stress is a subjective sensation associated with a varied of symptoms that differ from each of us, occurring to the American Institute of Stress. Signs of excess stress in someone's life include poor judgment, negative outlook, excessive worry, procrastination, increase alcohol and substance consumption. Scientist have found in animals that the transcription factor protein CREB is involved in the mechanism behind stress. In the research paper, "What Turns CREB ON," it states that stress is activated through the MEK/ERK/Ms1, p38/MK2, CaMKIV pathways (52). Dr. Carlson at Mclean Hospital, Harvard University, found that stress activates a chemical in the brain called CREB and that switching on CREB in key brain regions-therefore mimicking stress-made rats more sensitive to stressors and caused them to more quickly develop depressive like symptoms. Brunson found (35) found that in the hypothalamus and amygdala is differently modulated by single and recurrent stress, and is

determined also by the type of stress. A likely transcriptional regulatory factor for modulating corticotrophin releasing hormone (CRH) gene expression, the cAMP responsive element binding protein CREB, is phosphorylated (activated) in the developing **hypothalamus** within seconds of stress onset, preceding the transcription of the CRH gene and initiating the activation of stress-induced cellular and neuroendocrine cascades. Japanese scientist found alterations in neuronal gene expression mediated by an activation of cAMP response element binding protein (CREB) many play an important role in the pathogenesis of stress-related psychiatric disorders, such as major depression and posttraumatic stress disorder. They examined the influence of restraint stress on CREB phosphorylation in rat frontal cortex and hippocampus. Restraint stress significantly increased the levels of phosphorylation CREB (pCREB) in both regions of the brain. These findings suggest that the induction of pCREB may be involved in the pathogenesis of stress related psychiatric disorders (36). German scientist found chronic social stress significantly increased (by 45 to 120%) CRE/CREB driven gene expression in several brain regions (37). In 2009 scientists found in animals that have been re-exposed to fear or stressful stimuli, observed significant activation of CREB mediated gene expression in the hippocampus and amygdala. Also, these research scientist have found that when stress is introduced into the environment the transcription factor protein CREB is activated in healthy normal animals (38). A simple conclusion, I cannot activate CREB and maintain it through my interpretation of stress.

Dr. Mamiya observed Genetic disruption of CREB mediated transcription blocks both reconsolidation and long term extinction of contextual fear memory. Exposure to stressful stimuli caused significant activation of CREB mediated gene expression in the hippocampus and amygdala (39). Changes in catecholamine levels and expression of their biosynthetic enzymes are associated with stress related disorders such as elevated plasma norepinephrine in posttraumatic stress disorder and increased postmortem tyrosine hydorxylase in the Locus Coeruleus with major depression. Stress elevates tyrosine hydroxylase gene expression in the central nervous system (CNS). Increased transcriptional initiation was involved in the rat adrenal medulla and LC in response to repeated stress. In the LC, increased phosphorylation of CREB was observed after stress (40). Kwon (41) observed that the signal molecules c-Fos, phosphorylated extra cellular cell-regulated protein kinase (pERK), phosphorylated calcium/calmodulin dependent protein kinase II (pCaMKII) and phosphorylated cyclic-AMP response element binding protein (pCREB) in the hypothalamus and LC were increased by stress. The study revealed that pERK and pCREB up-regulated by repeated restraint stress were co-localized within many neurons of LC.

Published in the World Journal of Biological Psychiatry, 2011, June 23 (equb. ahead of print), entitled "Cyclic adenosine monophosate responsive element binding protein in post-traumatic stress disorder," by Dr. Claudia. His team tested CREB levels in Post traumatic patients. Blood samples were collected from patients and healthy control subjects on the same time and lympho-moncytes were isolated according to standardized methods. CREB protein levels and activation were measured by means of immunoezymatic techniques. The results showed that PTSD patients had statistically lower levels of total CREB protein in lympho-monocytes than healthy control subjects. On the contrary, no difference in the activated CREB protein was detected. These findings would suggest that the CREB pathway might be involved in PTSD.

In the journal Molecular Pharmacology, June 1, 2002, vol. 61, no. 6, 1453-1464, entitled, "Inducible and brain region specific CREB transgenic mice," by Dr. Sakai. They found chronic opiate or psycho stimulant administration up regulates the phosphorylation or expression of CREB in specific brain regions, such as the locus ceruleus or nucleus accumbens. Also, antidepressant, but not drugs of abuse, increase phosphorylation and expression of CREB in the hippocampus, and cerebral cortex, but not in nucleus accumbens or locus ceruleus. Antidepressants increased my sweating and insomnia (more in treatment section of paper).

Acetylcholine (Ach). Ach is a neurotransmitter in both the peripheral nervous system and the central nervous system. Scientist have speculated that Ach is the main neurotransmitter of eccrine sweating. Scientist have found that CREB antisense infusions into the amygdala may effect the modulation of memory in part through interference with norepinephrine and Ach neurotransmission in the amygdala (12). Extraneuronal Ach has been demonstrated to influence a plethora of cutaneous cell functions in an autocrine, paracrine and endocrine fashion. Through the differentiation-specific expression of its different nicotinic (nAch-R) and muscarinic (mAch-R) receptors. Ach acts upon keratinocyte proliferation and migration, terminal differentiation and barrier formation, sweat and sebum secretion as well as microcirculation and angiogenesis. Only very recently it has been recognized that acetylcholinesterase, but not cholineacetyltransferase, activity is regulated by H2O2. Considering that the outer layer of the

human skin can be a target for UV-generated H2O2 in the mill molar range, this mechanism needs to be taken into account for the regulation of Ach homeostasis in skin biology. There is a highly regulated distribution of Ach-R in human epidermis and adnexal structures, supporting previously observed effects of cholinergic compounds on keratinocyte biology. Most significantly, the regulated expression of Ach-R in sebaceous glands advocates a role for Ach in sebum production and as a production and as a promoter of sebocyte differentiation, thus offering an explanation for skin diseases associated with altered sebum production after chronic nicotine exposure. So far, Ach induced sweat production has been thought to be under the exclusive control of mAch-R. However, recently, the presence of both different nicotinic (nACh-R) and mACh-R in myoepithelial and acinar cells of eccrine sweat glands has been documented, indicating a more complex regulation of sweat production and expulsion (53).

Published in American Physiological Society 1981, page r45-r51, entitled "Pharmacologic responsiveness of isolated single eccrine sweat glands. Dr. Sato and team state that the eccrine sweat gland is unquestionably stimulated by cholinergic mediators. It is the general consensus that physiological sweating, either emotional or thermal, is mediated by acetylcholine released from the per glandular nerve endings or the postganglionic sympathetic fibers, with the justification that physiological sweating is always blocked by ant cholinergic agents. The maximal sweat rate was highest after stimulation with cholinergic agonists, was lower with the B-adrenergic agonist, and was least with the alpha adrenergic agonist.

The body makes a brain chemical Ach from Phosphatidylcholine. Researches think Phosphatidylcholine acts like a detergent and break down fat (Phosphatidylcholine increases sweating in hyperhidrosis patients). Dr. Burk at Albert Einstein College of Medicine (a researcher in hyperhidrosis) believes Ach is the main cause of hyperhidrosis. **He is dead wrong in his theory**. When I contacted Dr. Burk and told him he was wrong in his theory on hyperhidrosis, he was not very pleased. **Sweating.** Dr. Szabadi and team have shown that the sweat glands of patients suffering from anxiety neurosis are hypersensitive to intradermally injected carbachol, the dose response curve for carbochol obtained from anxious patients having a higher maximum than that obtained from healthy volunteers. The mechanism underlying this hypersensitivity is uncertain; however, the elevated maximum of the dose-response curve in the anxious patients suggests that anxiety states may be accompanied by a "sensitization" of normally "dormant" sweat glands. It was hypothesized that such a sensitization might be brought about by chronically raised sympathetic tone and or repeated acute episodes of excessive sympathetic discharge. Stress raised ambient temperature conditions both resulted in an increased responsiveness of sweat glands to carbachol. An effect of psychological stressors on the responsiveness of sweat glands to local pharmacological stimulation has not, to our knowledge, been reported previously. A possible explanation for this effect could be that the stressor evoked an increased rate of discharge in sympathetic fibres innervating the sweat glands, and that this resulted in a sensitization of the glands to carbachol. According to this explanation, the effects of both the psychological stressor and raised ambient temperature may be mediated by the same final common pathway, enhanced sympathetic outflow. Such a mechanism has previously been proposed to account for the heightened pharmacological responsiveness of sweat glands in patients suffering from anxiety neurosis. Of considerable interest for the understanding of the hyper-responsiveness of sweat glands in anxiety states is whether repeated or prolonged exposure to psychological stressors may give rise to a chronic hypersensitivity of sweat glands to the sympathetic transmitter. It seems possible that prolonged or repeated exposure to any variable (including anxiety provoking events) which produces sweat gland activation may result in long term changes in sweat gland sensitivity (42).

In another publication Dr. Szabadi and team found anxiety neurosis possessed a greater number of sweat glands, compared to healthy subjects, who had greater number of sweat glands which were capable or responding to carbachol. It is known that a considerable proportion of sweat glands are unresponsive to local pharmacological stimulation in normal subjects. The possibility some of these dormant glands become sensitized in anxiety states. Such a sensitization of sweat glands might be brought about bought about by raised sympathetic discharge in anxious patients. There is good evidence that the pharmacological responsiveness of sweat glands is influenced by activity in the innervating sympathetic fibres, since denervation results in hyposensitivity both to cholinoceptor and alpha adrenoceptor stimulants. Furthermore, repeated activation of sweat glands by local injections of cholinoceptor stimulants results in a progressive increase in pharmacological responsiveness (43).

Dr. Sato and team found evidence in the adult human axillae there exists a third type of sweat gland tentatively designated as the exocrine sweat gland. These exocrine glands are consistently present in adult

human maxillae regardless of sex or race. In the maxillae of the two 6 year old subjects, both classical apocrine and eccrine glands were present but no exocrine glands were found. Between 8-14 yr. of age, the number of large eccrine glands with or without partial segmental dilatation gradually increased. At 16-18 of age, the number of exocrine glands increased to as high as 45% of the total axillary glands. The data support that notion that apoeccince glands develop during puberty in the maxillae from eccrine or eccrine like sweat glands. It appears that the occurrence of the apoeccrine gland is limited to the hairy area of the axilla and is not found in the retroaxillary areas. Apoeccrine glands are extremely active in secreting fluid and electrolytes. Furthermore, they are more sensitive to adrenergic agents than average eccrine glands (44).

In another publication Dr. Sato and team found the exocrine glands showed a higher cholinergic sensitivity than eccrine sweat glands. The average total sweat rate of the exocrine gland for a 30 minute period was sevenfold higher than that of the eccrine sweat gland. In contrast, isolated apocrine glands showed intermittent pulsatile turbid sweat secretion. Thus exocrine sweat glands are functionally and pharmacologically distinct from axillary apocrine glands and significantly contribute to overall axillary sweating in humans. The Apoeccrine gland is many times larger than the adjacent eccrine sweat gland, and thus its secretory rate also many times larger than that of the eccrine sweat gland, but the Apoeccrine gland has one more important functional characteristic: it demonstrates a higher sensitivity (and thus a smaller K value) to methacholine stimulation (54).

Dr Sato found that in subjects classified as poor sweaters by history did respond very poorly to intradermal injection of **methacholine**. Sweat glands of poor sweaters tended to show lower pKa values, or in other words, lower cholinergic sensitivity, smaller glands, compared with those of the good sweaters. In fact, excellent correlation was found between cholinergic sensitivity of the sweat glands and sweat rates per gland (54).

Dr. Sato found the human axillary aprocrine glands are endowed with well-developed Myoepithelium, but its pharmacological responsiveness has remained unknown. The tubular contractions was induced by stimulation with phenylephrine or adrenaline **but not with isoproterenol or acetylcholine**. A higher concentration of acetylcholine produced a minor degree on contraction. The phenylephrine induced contraction was blocked by phentolamine by not by propranolol. It was concluded that the contractile response of the aprocrine Myoepithelium is selectively controlled by the alpha adrenergic stimulation but not to cholinergic or beta-adrenergic stimulation (55).

Dr Vaalasti and team found coexistence of the two neurotransmitters, acetylcholine and Vasoactive Inestinal Polypeptied (VIP), in the same nerves innervating both eccrine and apocrine sweat glands in human Maxillae (56).

Published in the British Journal of Dermatology (1991) 124, 547-549, entitled "Neuropeptides in skin disease: increased VIP in eczema and psoriasis but not axillary hyperhidrosis. Dr. Bloom and team found VIP concentrations was unchanged in skin affected by axillary hyperhidrosis. VIP may increase local blood flow in eczema and psoriasis, but does not appear to play a role in axillary hyperhidrosis. Increased Ach may stimulate post synaptic M1-muscarinic receptor to cause depressive behavior.

Published in American Journal of Med. Genet A, 2006 Mar 15; 140(6):567-72, entitled "Primary palmar hyperhidrosis locus maps to 14q11.2-q13. They found from the data of three of the 11 families examined, the combined maximum two point LOD scores of 3.08 and 3.16 were obtained at the D14S283 and D14S264 loci, respectively, on chromosome 14q11.2-q13, under an assumption that two liability conditions depend on age. These regions were ruled out in eight other families. Haplotype analysis of the three families supported that one of the PPH locus is assigned at minimum to about a 6-cM interval between D14S1070 and D14S990 and at maximum to about a 30-cM interval between D14S1070 and D14S70.

Diet. Trimethylaminuria is a disorder characterized by fish odor in the urine, breath, sweat and reproductive fluids of the person. These individual are unable to break down choline. Treatment is through dietary restrictions of Trimethylamine (found in milk), choline (present in liver, eggs, peas, peanuts, beans, soy products, brussels sprouts and broccoli), lecithin and lecithin containing fish oil supplements, and some types of seafood. Some studies have shown that copper chlorophyll supplements have been used to eliminate unpleasant odors.

In one study, subjects who had mild palmer sweating were given high Phosphatidylcholine meal, and after 12 hours, 10 out of 10 subjects produced more sweat with a high Phosphatidylcholine meal than with a low one. Subjects given lecithin also had a significantly increased sweat secretion (57). Lecithin is one of the best supplements to thin the bile so that toxins and chemical can flow out of the liver more easily. Lecithin also helps to break down fats and helps to detoxify a fatty liver. Lecithin is composed of choline,

inositol and linoleic acid.

The ABCB4 transporter gene (MDR3) regulates the secretion in bile of Phosphatidylcholine. A defective transporter gene makes bile toxic. A mutation of the ABCB4 gene can cause inadequate secretion of bile in the liver, leading to cirrhosis. Phosphatidylcholine protects the liver from toxic substance in the bile, low concentration can lead to liver damage (could suffers of hyperhidrosis have high levels of Phosphatidylcholine already in their system ????????) **Phosphatidylcholine increased my sweating and insomnia significantly**.

Reported in the Science Daily (Nov. 3, 2004), titled "High-Fat diets hammer memory, more than a waistline worry." In the article researchers at Kosair Children's Hospital Research Institute in Louisville, Kentucky, found that a diet high in fats and carbohydrates worsen cognitive deficits in rats exposed to repeated brief periods of low oxygen during sleep. In the work by David Gozal, MD, and his colleagues, adult male rats were fed either a diet high in fats and refined carbohydrates or a diet in fats and high in complex carbohydrates starting at postnatal day 30 and continuing for 90 days. They were then exposed to either normal levels of oxygen or brief periods of low oxygen (intermittent hypoxia) for 12 hours a day for 14 days. The investigators then measured levels of CREB phosphorylation, a measure of cellular tolerance to stress and of the ability to generated memory under situations of hypoxia, in different brain region. Rats in the normal oxygen group that ate a diet low in fats but high in complex carbohydrates showed normal levels of CREB phosphorylation in the hippocampus, a part of the brain involved in learning and memory. Rats in three other groups-intermittent hypoxia; high fat, refined carbohydrate diet: and intermittent hypoxia with high-fat, refined carbohydrate diet-showed substantial decreases in CREB phosphorylation. Rats in the intermittent hypoxia and the high fat, refined carbohydrate diet groups also had much more difficulty on a memory task that did rats exposed to intermittent hypoxia alone or fed the high fat, refined carbohydrate diet alone. "Our new findings provide the first support for the hypothesis that diet can modify an individual's vulnerability to cognitive impairments caused by these brief periods of low oxygen concentrations such as encountered in patients with sleep apnea," says Gozal. "These results suggests that an improved diet can be important part of the treatment regimen in patients with sleep apnea."

On a Celiac Disease website some suffers of Celiac Disease have anhidrosis (cannot sweat) and are easily overcome by heat and experience heat exhaustion. One women who had been on a gluten free diet for 2 years started to sweat normally while on this diet. Her nor her doctors have any idea as to why this has happened. Some suffers of Celiac Disease and anhidrosis have tried the amino acid tyrosine (tyrosine is synthesized from phenylalanine; phenylalanine is contained in Cholestyramine and Welchol-bile acid sequestrant) to increase sweating. One women noticed while taking tyrosine right before bed seamed to really help her get a deep sleep and able to remember her dreams. When she took it during the day it made her feel tired (Tyrosine did not help me sleep or my sweating, in fact it made my condition worse).

On a Veterinarian website for horses, a biochemist named Raymond LeRoy developed a supplement that starts anhidrosis horses to start to sweat. The supplement is called AC, and contains four ingredients, ascorbic acid, tyrosine, niacin and cobalt but. After about two weeks these horses where back to sweating normally. These veterinaries have no idea why some horses do not sweat, but researchers theorize that the sweat glands lose their ability to produce sweat when an excessive demand is place on them, either over time or by one traumatic episode of heat stress. Constant triggering of sweat gland receptors desensitizes them and makes them unresponsive to stimuli. Once damaged, the receptors rarely recover their original sensitivity, even over time. Microscopic examination of sweat glands of anhidrosis horses shows them to be contracted and occluded by necrotic cells, and likely result of their inactivity.

Published in Anesthesiology 2004; 100: 634-9, entitled "effect of amino acid infusion on central thermoregulatory control in humans. Dr. Nakajima and team discovered amino acid infusion increased the metabolic rate and the resting core temperature. However, amino acids also produced a synchronous increase in all major autonomic thermoregulatory defense thresholds; the increase in core temperature was identical to the set point increase, even in a cold environment with amble potential to dissipate heat. In subjects with intact thermoregulatory defenses, amino acid induced hyperthermia seems to result from an increased set point rather than increased metabolic rate per se.

An individual wrote on the internet, suffering from hyperhidrosis, and stated, "Hyperhidrosis can be caused by undiagnosed food intolerances or heavy metal poisoning. The two are not unrelated. I had severe hyperhidrosis along with arrhythmia, migraines and muscle twitching. I went through all the regular treatments including robinul, klonopin, dry sol, and finally ETS surgery. After 2-3 years the hyperhidrosis and Raynaud's Syndrome began to return. My symptoms were caused by mercury toxicity from old fillings, which led to wheat and dairy intolerance (gluten and casein).

After eliminating grains and dairy from my diet, the symptoms have gone away. I had all fillings replaced with composite material, and have been taking supplements for B vitamins, minerals (magnesium, zinc, etc) and probiotics. If you search, there are several sources which mention hyperhidrosis as a symptom of mercury poisoning. This can be related to wheat and dairy intolerance because mercury inhibits DPP-IV, the main enzyme needed to digest these foods. Heavy metals don't show up on regular tests until it is provoked out the body with a chelating agent. I wasted money on one blood test before finding another doctor who did a urine test properly. Sensitivity to gluten may result in neurological dysfunction, called gluten ataxia."

Published in the Science Daily (Apr. 30, 2002), "Sensitivity to gluten may result in neurological dysfunction; independent of symptoms." It stated in the article, you may have gluten sensitivity and not even know it. A loss of coordination (ataxia) may result from gluten sensitivity. This disease is known as gluten ataxia. The study found that some patients might never experience the gastrointestinal symptoms that prompt them to seek treatment for the disorder. "Gluten ataxia is a common neurological manifestation of gluten sensitivity," according to M. Hadjivassiliou, MD., of the Royal Hallamshire Hospital, Sheffield, UK. "It remains unclear why some patients with gluten sensitivity present solely with neurological dysfunction when others present with gastrointestinal symptoms (gluten sensitive enteropathy) or an itchy skin rash. Although the cerebellum (the part of the brain responsible for coordination) and in particular the Purkinje cells (output neurons of the cerebellum) appear to be most susceptible to damage in patients with gluten ataxia, other areas of the brain are not spared. "We were interested to determine the mechanism by which Purkinje cells are damaged in gluten ataxia," commented Dr. Hadjivassiliou. Study results show that patients with gluten ataxia have antibodies against Purkinje cells and also that antibodies against gluten (antigliadin antibodies) cross react with Purkinje cells. "These results strengthen our contention that eliminating these antibodies through strict adherence to a gluten free diet may have important therapeutic implication for patients with gluten ataxia, concluded Dr. Hadjivassiliou.

Enteroheptic Circulation. Enteroheptic circulation refers to the circulation of biliary acids from the liver, where they are produced and secreted in the bile, to the small intestine, where it aids in digestion of fats and other substances, back to liver. Endogenous bacteria play an important role in enter hepatic circulation.

Three minor sulfur containing arsenic metabolites: monomethylmonothiaorsonic acid (MMMTA (V)), Dimethylmonothiorsinic acid (DMMTA (V)), and dimethyldithioarsinic acid (DMDTA (V)) were recently found in human and animal urine after exposure to inorganic arsenic. However, it remains unclear how the thioarsenicals are formed in the body and then excreted into the urine. It is hypothesized that the generation of thioarsenicals occurs during enteroheptic circulation. Male rats with a deficiency of multidrug resistance associated protein 2 were orally administered a single dose of inorganic arsenic. Five hours dosing less than 1% of the dose was recovered in the bile of rats. 3 to 6 hours after dosing arsenic levels in liver, red blood cells and plasma were higher than normal rats. In normal rats, in urine, significant levels of MMMTA (V) and DMMTA (V) were detected. Rats with a deficiency MDR2 only had DMMTA (V) were detected. The present results of the metabolic balance and speciation study suggests that the formation of MMMTA (V) and DMMTA (V) in rats is dependent on enteroheptic circulation. In addition, in vitro experiments indicated that arsenicals excreted from bile may be transformed by gastrointestinal microbiota into MMTA (V) and DMMTA (V), which are then absorbed into the bloodstream and finally excreted into the urine (3).

Methylated trivalent species monomethylarsonous acid (MMA III), dimethylarsinous acid (DMA III) are more catatonic that arsenic acid.

Multidrug Resistance Associated Protein (MRP). The transport of arsenic into bile depends on the multidrug resistance associated protein 2 (MRP2/cMOAT) transport and that glutathione is obligatory for such transport. They demonstrated that two arsenic-glutathione complexes not previously identified in vivo, arsenic triglutathione and methyl arsenic diglutathione, account for most of the arsenic in the bile. Although arsenic can be rapidly cleared from the body, the factors that control its transport into bile and feces are largely unknown. Previous studies of the clearance of inorganic arsenic have demonstrated that presence of arsenite, arsenate, monomethylarsonic acid (MMA), and dimethylarsenic acid (DMA) in feces and urine, but these studies have not illuminated the molecular basis for transport or the nature of the transported products. GSH has been suggested to be important as an intracellular reluctant for arsenic methylation and in arsenic transport. MRP2/cMOAT is highly expressed in the bile canaliculus of hepatocytes and mediates hepatobilliary transport of many organic compounds including GSH. Based on these observations, we hypothesized that the transport of arsenic and its methylated derivates might depend on the formation of arsenic GSH complexes and their transport by MRP2/cMOAT. The hepatobilliary

transport of arsenic depends on the bile canalicular MRP2/cMOAT transporter. Also MRP2/cMOAT transports GSH and GSH conjugates and arsenic is transported by this mechanism as well. Two GSH complexes not previously identified in vivo, arsenic triglutathione and methyl arsenic diglutathione, account for most of the arsenic in the bile. Their findings raise the possibility that arsenic GSH complex formation and transport by multidrug-resistance proteins represent a general process by which cells clear arsenic. MRP2 is one of a family of multidrug resistant proteins, some or all of which may be involved with arsenic transport. Protein restricted diets reduce liver GSH levels. We do not know precisely how much lowering GSH is necessary to begin to reduce levels of excreted arsenic, but the observed increased toxicity of arsenic in humans on protein deficient diets may result from less formation of arsenic GSH complexes and less excretion (7).

Gallstones and Bile Acid. The recurrent micolithiasis represents one of the frequent clinical forms of lithiasis of the bile ducts. This affection is characterized by the presence of cholesterol micro gallstones on hepatic canaliculars, and belongs to a heterogeneous group of autosomal recessive liver disorders. Radioligical diagnosis can be confirmed by analysis of MDR3 gene, coding protein involved in physiologic translocation of phospholipids in bile discovery of MDR3 mutation is of particular interest, since normally associated with good effectiveness of medication by urosdesoxycholic acid (58).

The human MDR3 gene is a member of the multidrug resistance (MDR) gene family. The MDR3 P-glycoprotein is a transmembrane protein that translocates phosphatidylcholine (regulates the secretion of phosphatidylcholine). The MDR1 P-glycoprotein related transports cytotoxic drugs. **It's over expression can make cells resistant to a variety of drugs**. An increased directional transport of several MDR1 P-glycoprotein substrates, such as digoxin, paclitaxel, and vinblastine, through polarized monolayers of MDR3-transfected cells. Transport of other good MDR3 P-glycoprotein-dependent transport of a short-chain Phosphatidylcholine analog and drugs was inhibited by several MDR reversal agents and other drugs, indicating an interaction between these compounds and MDR3 P-gp. Cell membranes from Sf9 cells over expressing MDR3 showed specific MgATP binding and a vanadate-dependent, N-ethylmaleimide-sensitive nucleotide trapping activity, visualized by covalent binding with [alpha-(32)P]8-azido-ATP. Nucleotide trapping was nearly abolished by paclitaxed, vinblastine, and the MDR reversal agent's verapamil, cyclosporine A, and PSC 833. We conclude that MDR3 P-glycoprotein-mediated transport is low for most drugs, explaining why this protein is not detectably involved in multidrug resistance. It remains possible, however, that drug binding to MDR3 P-glycoprotein could adversely affect phospholipid or toxin under conditions of stress (59).

In the formation of cholesterol gallstones, cholesterol hyper secretion into bile causing cholesterol supersaturation and crystallization appears to be the primary factor, with disturbed gallbladder and intestinal motility as secondary factors. Although intestinal uptake mechanisms have not yet been fully elucidated, the HDL receptor scavenger receptor B1 (SRB1) may be involved. Since HDL-cholesterol, both from the intestine and peripheral sources, is the preferred type of cholesterol for biliary secretion, increased HDL transport to the liver can also cause cholesterol hypersecretion in bile. In the hepatocyte, bile formation is regulated by several transmembrane proteins, all belonging to the ABC family. A change in the activity in one of these proteins can have a profound impact on biliary lipid secretion. The bile salt export pump (BSEP or ABCB11) regulates the excretion of bile salts into bile and mutations cause severe homeostasis. The second ABC transporter, ABCB4 (MDR3) regulates the secretion in bile of Phosphatidylcholine (PC), while ABCG5/G8 is active in the excretion of cholesterol and sterols into bile. These transporters also facilitate transport of sterols back into the intestinal lumen. Mutations in either of these genes cause sitosterolaemia with increased absorption of plant sterols and cholesterol. Until now, evidence for genetic background of human gallstones disease is mostly indirect and based on ethnic differences. Only two single gene defects are associated with gallstones. One is an ABCB4 mutation which causes a deficiency in biliary PC secretion and the other is a CYP7A1 mutation, the rate-limiting enzyme in the synthesis of bile salts from cholesterol in the liver. Recently, several common DNA polymorphisms in the ABCG8 gene were discovered that are associated with variations in plasma sterols, which could also influence biliary cholesterol secretion, but there is still a paucity of human studies (60).

Published in the Science Daily, October 24, 2008, scientist discovered that a mutation of the ABCB4 gene can cause inadequate secretion of bile in the liver, giving rise to cirrhosis. The gene ensures the production of a transporter protein that is responsible for the excretion of Phosphatidylcholine into bile. **Phosphatidylcholine protects the liver from toxic substances in the bile, a low concentration can thus lead to liver damage.**

Published in Toxicology Science, 2004 Dec; 82(2):478-87, entitled, "Arsenic speciation in bile and

urine following oral and intravenous exposure to inorganic and organic arsenic in rats." It stated although inorganic arsenate (iAsV) and arsenite (iAsIII) are metabolized in the liver and excreted into bile and urine, the metabolites in the bile after the oral intake of iAs remain unclear. Male rats were orally (po) and intravenously (iv) exposed to iAs and methylated arsenics, and arsenic speciation in the urine and bile analyzed. Arsenic caused induction of multidrug resistance protein (MRP2) and changes in gluthione (GSH) levels in the liver and bile were also determined. The metabolic speciation studies revealed that arsenic was excreted into bile in the methyl arsenic-diglutathione (MADG) and/or dimethylarsenic acid (DMAV) forms in iAsIII or iAsV-po rats, but that MADG and arsenic-triglutahiione (ATG) are the main forms excreted into bile in iAsIII and iAsV-iv rats. In MADG-po rats, the MADG was excreted into bile in the MADG and DMAV forms. Monomethylarsonic acid (MMAV) and DMAV-iv rats did not excrete significant amounts of either MMAV or DMAV into bile and mostly excreted into urine in the unchanged chemical forms. Taken together, the DMAV detected in the bile is mostly supposed to be the dissociation of Dimethylarsenic-glutathione (DMAG). Urinary arsenic speciation showed that arsenic metabolized to 43% methylated DMAV, 47% unmethylated iAsIII, and 10% iAsIII in iAsIII-iv rats, whereas only 3% methylated DMAV, 87% unmethylated iAsV, and 10% iAsIII were detected in iAsV-iv rates. Arsenic was accumulated does dependently, and arsenic concentration was significantly higher in the iAsIII-po rat liver than in the iAsV-po rat liver. GSH levels in the bile were decreased by relatively higher doses of iAsV-po, but significantly increased by iAsIII or iAsv-iv. Arsenic exposure increased the expression of MRP2 in the liver. Pretreatment with Buthionine Sulfoxime predominantly inhibited the arsenic excretion into bile in iAs-iv rates. Our data demonstrated that biliary and urinary arsenic excretion and speciation are affected by the route, dose, and chemical forms of arsenical administration, and GSH plays a key role in arsenic metabolism. We are also first to show that DMAV that probably originated from DMAG is excreted into bile in iAs-po rats.

Intrahepatic Cholestasis Pregnancy (ICP) is typically occurs with troublesome itching of the palms and feet without presence of rash. The genetic mutation occurs in the hepatocellular transport protein ABCB4 (MDR3), which controls secretion of Phosphatidylcholine into bile. A defective Phosphatidylcholine translocation leads to a lack of Phosphatidylcholine in bile. Phosphatidylcholine normally accompanies bile acids, preventing damage to the biliary epithelium. In ICP, serum bile acid levels are grossly elevated and serum cholesterol levels are typically not elevated. **Treatment with ursodeoxycholic acid and Cholestyramine**.

The pathogenesis of acute cholecystitis (AC) is controversial. Bile acids may be involved in the pathogenesis of AC because the hydrophobic chenodeoxycholic acid (CDCA) reproduced in vitro the muscle dysfunction observed in AC and was prevented by the hydrophilic urodeoxycholic acid (UDCA). The present study examined the in vivo effect of UDCA or CDCA on gallbladder muscle dysfunction caused by AC. Guinea pigs were treated with placebo, UDCA, or CDCA for 2 weeks before sham operation or induction of AC by bile duct ligation (BDL) for 3 days. Pretreatment with oral UDCA prevented the defective contraction in response to agonist (acetylcholine-ACH), cholecystokinin 8 (CCK-8) and KCI) that occurs after BDL. Prostaglandin (PG) E (2)-induced contraction remained normal in the placebo and UDCA-treated groups but was impaired in the CDCA-treated group. Treatment with UDCA also prevented the expected increase in levels of H2O2, lipid per oxidation, and PGE(2) content in the placebo-treated AC group, whereas CDCA caused further increases in these oxidative stress markers. The binding with UDCA enriched gallbladder bile acids with its conjugates and reduced the percentage of CDCA conjugates. In contrast, treatment with CDCA significantly decreased the percentage of UDCA in bile. In conclusion, oral treatment with UDCA prevents gallbladder muscle damage caused by BDL, whereas oral treatment with CDCA worsens the defective muscle contractility and the oxidative stress (61).

Bile acids (BA) are a group of structurally diverse molecules that are primarily synthesized in the liver from cholesterol, are the chief components of bile. Besides there well established roles in dietary lipid absorption and cholesterol homeostasis, it has recently emerged that BA are also signaling molecules, with systemic endocrine functions. BA activate mitogen activated protein kinase (MAPK) pathways, are ligands for the G-protein coupled receptor (TGR5), and activate nuclear hormone receptors such as farnesoid X receptor alpha (FXR). Through activation of these diverse signaling pathways, BA can regulate their own enter hepatic circulation, but also triglyceride, cholesterol, energy, and glucose homeostasis. Bile consists of BA, cholesterol, Phosphatidylcholine and Bilirubin, and is secreted from the hepatocytes into the bile canaliculated. In the liver, the BA are taken up at the basolateral (sinusoidal) membrane and exported again at the apical (canalicular) membrane of the hepatocytes into the bile canaliculus (transhepetic BA flux). This completes their Enterohepatic circulation. Each BA molecule

may complete 4-12 cycles between the liver and intestine per day. Owing to this efficient recirculation, only a small amount of the BA pool size is derived from de novo biosynthesis (62).

The discovery of BA as the endogenous FXR ligands suggested a function for them in the enter-hepatic recycling of BA and the feedback regulation of BA biosynthesis, which is in line with the reported expression pattern of FXR in liver and intestine. In these tissues, FXR activation protects against accumulation of BA, which is toxic, via mechanisms that have been reviewed recently. FXR activation in the liver leads to increased conjugation of BA, followed by the excretion of BA from the hepatocyte into the bile canaliculus, leading to an increase in the formation of bile. FXR is a BA sensor that protects the liver from accumulation of toxic BA and xenobiotics (62).

High Transhepatic BA flux, which translates in FXR activation, positively correlates with hepatic and LDL cholesterol levels, since cholesterol is not eliminated via its conversion to BA. HDL levels are negatively correlated with Tran hepatic BA flux. BA also effect triglyceride homeostasis. There in an inverse relationship between the Tran hepatic BA flux and hepatic very low density lipoprotein (VLDL) production. Treatment with BA binding resins, ileal exclusion, or bile withdrawal interrupts the enterohepatic circulation, decreasing Tran hepatic BA flux (62).

FXR deficient mice display elevated serum levels of triglycerides and high density cholesterol, demonstrating a critical role of FXR in lipid metabolism. FXR deficient mice display both impaired glucose tolerance and decreased insulin sensitivity, activation of FXR improves hyperglycemia and dyslipidemia in vivo in diabetic mice (63).

Treatments

There is an embarrassing nature about this condition, where affected individuals are reluctant to discuss this condition with others or seek treatments. There are numerous conservative therapies used in the treatment of hyperhidrosis, including antiperspirants, tap water Iontopheresis, botulin toxin A, anticholinergic drugs, and psychotherapy. Most patients seldom find permanent relief from these approaches, are usually transient and successful only for mild cases (64).

Treatment options should concentrate on the different areas of hyperhidrosis, such as palmer, axillary/planter, planter, axillary, facial/planter/axillary etc. One treatment option that is successful in treating one area of hyperhidrosis my not be effective in treating another; this should be taken into consideration.

Over the years I have tried many different types of treatments for my debilitating hyperhidrosis, all of which had limited results, from controlled breathing techniques, relaxation techniques, hypnosis, cognitive behavior techniques and prescription medication. For example, hypnosis and relaxation tapes worked great for a short period of time. Every day I would listen to the relaxation tape and slowly over the coming days my sweating and insomnia improved. I was so happy and excited that I found something that was controlling my sweating and insomnia. This feeling only lasted a few days, and within a 12 hour period my disorder reappeared. During this period of time my sweating and insomnia became worse than before I started the treatment. Over the next few days I analyzed the past days events thinking I was exposed to a toxic chemicals or ate the wrong food. I soon realized no revealing evidence that caused this turn of events. Only now do I know what caused this strange reversal. That is, I cannot activate and maintain the CREB protein in times of stress and that these types of treatments only put a temporary dam on the HPA axis. Once I am exposed to stressful stimuli all the major neurotransmitters are activated to a higher level, trying once again to increase CREB.

Vitamins. Samuel and team found rats treated with arsenic had significantly higher level of oxidized protein as assessed by increased carbonyl residues and decreased protein thiols (protein sulfhydryl) as compared to control rats in the cortex, striatum, cerebellum, hypothalamus and hippocampus. Alpha Lipoic Acid resulted in reversal of the arsenic induced treads. Lipoic acid treatment reduces oxidative protein damage in arsenic intoxicated rat brain regions (19).

Arsenic exposure elicited a significant decline in glutathione content and in the activity of related enzymes, with the greatest decreases seen in the cortex, striatum, and hippocampus. Highly elevated content of the thobarbituric acid reactive substance malondialdehyde (MDA) in the brain regions of arsenic exposed rats reflected extensive lipoid per oxidation (LPO) processes. Lipoic acid treatment was effective

in reducing brain regional arsenic levels and lipid per oxidation and in increasing glutathione content and the activity of its related enzymes. Lipoic acid, by acting as an alternative sulfhydryl nucleophile to glutathione, prevents its oxidation to glutathione disulfide in detoxifying reactions against ROS and consequently increases the activity of glutathione related enzymes (21).

Inorganic arsenic deposition was found to be most significant in heptic tissue and neuronal cells of rats treated with arsenite. Antioxidant levels in heptic and neuronal cells were reduced significantly by the induction of arsenic. Quercetin was found most potent for a complete prevention of arsenite induced reduction in antioxidant levels in the liver and brain of rats. Arsenic induced a substantial increase in heptic hydorxyproline (HP) and quercetin treatment resulted in complete replenishment of the HP level to normal. Quercetin completely prevented the arsenite induced up regulation of cytochrome c expression in liver and brain significantly that the protective effects of quercetin could be related to the reduction of arsenic deposition in both organs (22).

The study investigated the distraction of selenium, magnesium and calcium with arsenic on blood biochemistry and oxidative stress. Selenium was the most effective in reducing arsenic induced inhibition of blood delta aminolevulinic acid Dehydrates (ALAD) activity and liver oxidative stress. Calcium and magnesium also showed favorable effects on hematological and other biochemical parameters. Because selenium was the most effective, it should be added to chelation therapy to achieve the best protective effects against arsenic poisoning in humans (23).

Folic acid supplementation to participants with low plasma concentrations of folate lowered blood arsenic concentrations, primarily by decreasing blood MMAs and increasing urinary DMAs. Therapeutic strategies to facilitate arsenic methylation, particularly in population with low folate deficiency or hyperhomocysteinemia or both, may lower blood arsenic concentrations and thereby contribute to the prevention of arsenic induced illnesses (24).

Inorganic arsenic is metabolized to monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), and this methylation facilitates urinary arsenic excretion. Arsenic is methylated in a S-adenosylmethionine (SAM) dependent process. The methyl group from SAM is derived from folate or from choline or betaine. The first methylation step is the oxidative methylation of arsenic to monomethylarsonic acid (MMAv), which can then be reduced to monotheylarsonous acid (MMAIII). MMAIII is then methylated to dimethylarsinic acid (DMAv). It is not currently know to what extent DMAv is then reduced to dimethylarsinous acid (DMAIII), in vivo, because this is reported to be an unstable intermediate. Inadequate methylation of arsenic is associated with greater arsenic toxicity. In animal, methyl-deficient diets have resulted in reduced arsenic methylation and higher tissue concentrations of arsenic. The trivalent metabolites MMAIII and DMAIII may be more toxic than the pentavalent forms of organic arsenic, suggesting that methylation itself may increase arsenic toxicity. Nevertheless, by facilitating urinary arsenic excretion, methylation reduces tissue exposure. Thus, complete methylation to DMA may reduce tissue exposure to arsenical compounds despite the transient production of trivalent metabolites. Previous studies suggest that persons with more complete methylation, characterized as greater proportions of DMA and lesser proportions of MMA and inorganic arsenic in urine, have a lower risk of adverse arsenic related health outcomes. Higher intake of cysteine, methionine, calcium, protein, and vitamin B-12 were associated with lower percentages of inorganic and higher ratios of MMA to inorganic in urine. Higher intake of niacin and choline were associated with higher DMA to MMA ratios (**niacin and choline increase my sweating significantly) (25).**

Curcumin protects arsenic induced neurotoxicity by modulating oxidative stress, neurotransmitter levels and dopaminergic systems in rats. Arsenic chronic exposure to arsenic has been associated with cognitive deficits in humans, the present study has been carried out to implore the neuroprotective potential of curcumin in arsenic induced cholinergic dysfunctions in rats. Rats treated with arsenic (sodium arsenite) exhibited a significant decrease in the learning activity, assessed by passive avoidance response associated with decreased binding of (3) H-QNB, known to label muscarinic cholinergic receptors in hippocampus and frontal cortex. Decease in the activity of acetyl cholinesterase in hippocampus and frontal cortex, immunoreactivity of choline acetyltransferase (ChAT). Curcumin improved all activity in the rat brain (26).

Sodium arsenite significantly decreased the activities of antioxidant enzymes, SOD, CAT, glutathione S-transferase, glutathione reductase and glutathione peroxidase, the level of cellular metabolites, reduced glutathione, total thiols and increased the level of oxidized glutathione. In addition it enhanced the levels of lipiod per oxidation end products and protein carbonyl content. The treatment with Arjunolic Acid at a dose of 20 mg almost normalized above indices (27).

People vary greatly in the degree to which they methylate inorganic arsenic, and recent evidence suggests that those who excrete high proportions of ingested arsenic as monomehtylarsenic (MMA) are more susceptible that others to arsenic caused cancer. Subjects that lower intake of protein excreted a higher proportion of ingested inorganic arsenic as MMA and lower proportion as DMA that did subjects in the upper quartile of protein intake. Subjects in the lower quartile of iron, zinc, and niacin intake also had higher urinary percent MMA and lower percent DMA levels than did subjects with higher intakes of these nutrients. The findings are consistent with the theory that people with diets deficient in protein and other nutrients are more susceptible than others to arsenic caused cancer (28).

Dr. Mark Hyman, published in the Huffington post healthy living, entitled, "how to rid your body of mercury and other heavy metals: A 3 step plan to recover your health. His plan goes into great detail how to get rid of heavy metals.

Chelation. Ethylenediaminetetraace acid (EDTA) is a IV chelation therapy used to treat acute and chronic lead poisonings by pulling toxins (such as lead, cadmium, mercury and arsenic) from the bloodstream. EDTA promotes the excretion of toxin through the kidneys. No form of EDTA protects the body from oxidative stress or replenishes depleted glutathione and antioxidant levels. EDTA in its function as a chelator mobilizes lead, cadmium and arsenic and can redistribute these mobilized metals in the body. It's like stirring up the soup pot and letting it all settle back down to wherever it may. **This can lead to adverse side effects, particularly in a person whole glutathione and anti-oxidant levels are depleted** (suffers of hyperhidrosis have low levels of glutathione. This might be an indication that are bodies are trying to remove heavy metals.

Antibotics. Chaudhary and team found the drug Sulbactomax-combination of Ceftriaxone and Sulbactam antibiotics along with a third vector VRP 1034, increases the antioxidant levels in the body and protect against arsenic induced toxicity. Cephalosporins (**Ceftriaxone or Roceptin**) are known thioether containing class of antibiotics which are more effective in preventing the free radical mediated oxidation of sulfhydryl groups in the antibiotics. Besides free radical scavenging property and antimicrobial effect, Ceftriaxone and Sulbactam individually interact with arsenic ions and other heavy metals and form complex which chelate out from sulfhydryl group of antibotics. Combination of Ceftriaxone plus Sulbactam with VRP 1034 (Sulbactomax) is the most active drug which enhanced the free radical scavenging property and also enhanced the removal of heavy metal ions (14).

Bile acids. Bile acids could be a potential treatment for hyperhidrosis. In one study on psoriasis, scientist successfully treated psoriasis patients with bile salts. I believe psoriasis is a stress disorder similar to hyperhidrosis, and treatments that are successful treating patients suffering from psoriasis could possible help hyperhidrosis sufferers (for example, the drug Topirmate, listed below has positive effect on hyperhidrosis and psoriasis patients). Hyperhidrosis patients need to find a pathway that activates CREB without activating or suppressing the HPA axis, like many of the psychiatric drugs on the market today.

Scientist have found that bile acid, Urodeoxycholic acid (UDCA) in conjugated with Taurine in vivo to form Tauroursodeoxycholic acid (TUDCA) resulted in phosphorylation of CREB. It usually prescribed to patients with Cholestatic disease. UDCA confers protection in hepatocytes, such as modulation of mitochondrial membrane integrity, replenishment of glutathione, and activation of transcription factors. TUDCA is activity secreted into the canalicular bile. TUDCA phosphorylated and trans activates CREB in biliary epithelial cells. Various intracellular signaling pathway can activate CREB. Originally described as a target of the cAMP/PKA pathway, CREB has been found to be activated by Ca2+ signals and Ca2+/calmodullin dependent protein kinase and to be phosphorylated by kinases of the MAPK pathway (65).

Scientist have found in psoriasis patients low bile production. Bile acids are produced by the liver and storage by the gallbladder. Bile enhances the detoxification of certain toxins. In some patients after the gallbladder is removed these people develop psoriasis. Scientist have tested the hypothesis that the deficiency of bile acids and the consequent induction translocation might play a role in psoriasis. Treatment with oral bile acids has shown improvement in psoriasis patients (66).

In three Japanese patients with psoriasis associated with nonalcoholic fatty liver disease in which the skin lesions dramatically resolved after treatment of the fatty acid liver disease with ursodeoxycholic acid (UDCA). According to the literature, arachidonic acid is released from phospholipase A (2) (PLA (2)) and is a precursor of eicosanoids, including prostaglandins, leucotreines, and thromboxanes, which are potent inflammatory mediators. PLA(S) activity has been reported to be significantly raised in the serum and skin tissue of patients with psoriasis. UDCA has been reported to suppress the increased activity of group IIA PLA (2), a secretory low molecular weight PLA (2) (PLA (2) IIA0, in HepG2 cells (a human

hepatoblastoma derived cell line) and in gallbladder and gallbladder bile samples from patients with cholesterol stones. Thus, UCDA may improve the skin lesion of patients with psoriasis by suppressing PLA (2) IIA activity (67). **UDCA (Ursodiol, Actigall) is used to treat gallstones**.

On the internet, titled "metacard for Tauroursodexoycholic acid TUDCA." It states TUDCA is a bile acid formed in the liver by conjugation of deoxycholate with the amino acid Taurine, usually as the sodium salt. TUDCA is able to prevent apoptosis and protect mitochondria from cellular elements that would otherwise interfere with energy production. One of these elements is a protein called **Bax** (Bcl-2-associated X protein or Bax is a protein of the Bcl-2 gene family). TUDCA plays an important role in preventing Bax from being transported to the mitochondria. Bile acids are steroid acids found predominantly in bile of mammals. The distinction between different bile acids is minute, depends only on presence or absence of hydroxyl groups on position 3, 7, and 12. Bile acids are physiological detergents that facilitate excretion, absorption, and transport of fats in the intestine and liver. Bile acids are also steroidal amphipathic molecules derived from the catabolism of cholesterol. They modulate bile flow and lipid secretion, are essential for the absorption of dietary fats and vitamins, and have been implicated in the regulation of all the key enzymes involved in cholesterol homeostasis. Bile acids recirculate through the liver, bile ducts, small intestine and portal vein to form an Enterohepatic circuit. They exist as anions at physiological pH and, consequently, require a carrier for transport across the membranes of the enterohepatic tissues. The unique detergent properties of bile acids are essential for the digestion and intestinal absorption of hydrophobic nutrients. Bile acids have potent toxic properties (e.g. membrane disruption) and there are a plethora of mechanisms to limit their accumulation in blood and tissue.

Taurine is an organic acid and is major constituent of bile. It is a conjugator of bile acids, helps increase cholesterol elimination in the bile, helps with fat absorption and elimination of toxins.

If you have **Candida a systemic fungal infection**, it produces an amino acid, beta alanine, which competes with taurine for reabsorption in the kidney. This causes you to lose taurine through your urine; an increase of taurine in urine actually means low taurine in body. **Candida produce over 80 different poisons** in the body some of these toxic substance are acetaldehyde and ethanol. Acetaldehyde is extremely toxic to the brain causing memory loss, depression, problems concentrating and fatigue.

Other

Hydrogen Sulfate (H2S). Some people appear to be intolerant to many foods and supplements containing sulphur, including B vitamins. This also includes glutathione shots and oral lipoceutical glutathione. There are bacteria in the small and large intestine that convert (reduce) sulphate compounds from sulphur containing foods and supplements to hydrogen sulphide (H2S) gas. Excess H2S is a potent neurotoxin affecting both the brain and nervous tissue. Candida yeast also produces some H2S gas when if ferments carbohydrates. If someone is having difficulty with all sulphur containing substances except taurine and sulfate, the problem may be at the sulphite oxidase step in the metabolism of sulphur. All chemically reduced forms of sulphur except taurine must eventually pass through this step to get to sulphate, the most oxidized form of sulphur. Excess sulphate is excreted in the urine, as is excess taurine. In some rare cases, the problem at the sulphite oxidase step is genetic, involving the formation of the active form of molybdenum (molybdopterin). People with this problem have severe diseases. However, in many cases, just taking more molybdenum will help. Molybdenum is the cofactor for the enzyme sulphite oxidase, Molybdenum is also a cofactor for two other enzymes in the body, xanthine dehdrogenase and aldehyde oxidase. People with molybdenum deficiency therefore can have low urate (uric acid) levels as well as **intolerance to alcohol**. Sulphate is required for: mucin protein (mucin protein is very important, if there is a deficiency in sulphation there are known links gut dysfunction. There must be enough sulphur attached to these proteins otherwise the gut wall will allow peptides through), steroids, bile acids, phenols, cholecystokinin (this protein allows the gut to be linked with the brain structure. This stimulates the secretion of enzymes, gastric acid, gallbladder contraction and controls food intake), gastrin (must be

sulphated to release active pepsin. Pepsin activates secretion release and cholecystokinin, which when sulphated, stimulates the pancreas to release pancreatic enzymes), catecholamine and the formation of connective tissue. Large amounts of sulphate are excreted via kidneys (defective sulphate transporter genes: NaSi-1) and intestines (leaky gut). H2S reduces the RAF/MAPK kinase/ERK signaling pathway.

Reported in the American Journal of Medical Science, 1993, Nov; 306(5):301-5, a case report found an oil well tester was rendered semiconscious by hydrogen sulfide. Over the next few days he experienced leg shaking, dizziness, sweating, trouble sleeping, and nightmares prevented his return to work.

Chemist treat ground water contaminated with hydrogen sulfide, with **hydrogen peroxide** and sodium hydroxide (leaves a yellow stain on fabric, might explain funny looking stain on underwear?????)

Dr. Matt Whiteman from the Peninsula Medical School, Exeter, England, stated, "We have known for years the H2S levels in tissue and blood are substantially elevated during inflammation. It was assumed that this was a bad thing. However, our research is suggesting that levels of H2A could be elevated as part of the body's way to limit and resolve inflammation."

Low levels of long term exposure to H2S are insomnia, depression and poor memory.

Sleep. CREB is an activity dependent transcription factor important for synaptic plasticity and memory storage. Levels of phosphorylated CREB (pCREB) within the cortex are higher in waking than in sleep, suggesting that CREB plays a role in sleep/wake regulation in mammals. The scientist tested the hypothesis that CREB is critical for sleep/wake regulation by examining behavioral state parameter in mice lacking alpha and delta isoforms of CREB. Over 24h, time spent awake was significantly decreased in CREB alphadelata mutant mice by approximately 100 min, and time spent in nonrapid eye movement sleep (NREM) sleep was increased correspondingly. Wake and REM sleep periods were shorter in CREB alpha delta mice, and CREB alpha delta mice had decreased levels of activity during wake and REM sleep, consistent with an impairment in the ability during wake and REM sleep, consistent with an impairment in the ability to maintain an activated electroencephalogram. These results suggest that the CREB protein contributes to the mechanisms by which wakefulness is maintained and demonstrate that specific genetic alterations in species as diverse as Drosphila and mice produce similar phenotypes in arousal and wakefulness. These scientist also found that afferent input form the LC, one of the primary sources of noradrenaline in the mammalian CNS, has been shown to play a key role in the pCREB (68).

In the book "No More Sleepless Nights", by Dr. Peter Hauri, a sleep specialist from the Mayo Clinic, found that if your insomnia is associated with depression, sleep curtailment also might help your depression. Doctors B. Pflug and R Toelle, two German researchers, found that going without sleep for an entire night helped many depressed patients. Instead of feeling sleepy, they became energized. These researchers treated patients by first keeping them awake at night, then letting them sleep normally for two or three nights until their depression started again, then keeping them awake another night, and so on. Some patients use this technique in the several weeks it takes before antidepressant medication starts to work; others are helped by the sleep deprivation alone. I believe going without sleep increases the CREB protein and my insomnia is a result of my body trying to activate CREB. Also stated in the book, cocaine or amphetamines cause a reduction in delta sleep and reduced REM sleep as well as insomnia (I experience the same effect, evidence in sleep study).

Bacteria or viruses have been shown to induce cytokines that modify immune response as well as sleep. But relationship between cytokines and sleep are complex, low doses of interleukin-1 (cytokine) increase NREM sleep in rats, but at slightly higher doses, it increase NREM sleep in rats only during the night, when rats should be awake. Still higher doses inhibit sleep both day and night. In other words, the same compounds does different things depending on the amount of the compound.

Also, in chronic alcoholics, sleep patterns are quite abnormal. Their sleep is usually very disrupted, often with hundreds of awakenings in a night. In fact, chronic alcoholic patients show a prematurely aged sleep, characterized by many awakenings, little or no delta sleep, and decreased REM sleep. Sleep is fragmented and shallow, total time in bed often is increased, the sleep-wake rhythm is blurred, and patients may show excessive daytime sleepiness (once again very similar to what I experience).

In Dr. Hauri's, book he states that most cases of insomnia, there is **hyper arousal**, that is, the whole person, both physically and psychologically, seems to be going at a higher speed. There is increased muscle tension, increased metabolism both day and night, and increased metal activity. In 1995, Doctors Michael Bonnet and Donna Arand, a husband-wife research team from Dayton, Ohio, found that insomniacs have an increased 24-hour metabolic rate (shown by measuring oxygen and carbon dioxide exchange) compared with normal sleepers. The author's also discusses that the brain does not seem to know that we are dreaming, but still gives commands to our muscles to carry out the actions we dream

about. Luckily, just before dreaming starts, a nucleus of nerve cells deep within the brainstem relaxes all our muscles so deeply that they are practically paralyzed. During dreaming, our brain's commands to move these muscles resulting only in very little movements, and this lets us sleep through our dreams.

A patient of the author who suffered from depression was admitted for three nights in the sleep lab. She averaged about 35 awakenings per night in the lab and less than four hours of total sleep. Much of it was stage 1; there was no delta sleep, and other characteristics of the sleep pattern were typical of depression. For example, the first REM period occurred ten minutes after she fell asleep, which often is a sign of depression, just as early morning awakenings are. She was given antidepressant and her sleep immediately improved. Prior to LD, this person's sleep pattern describes the sleeping pattern I mostly experienced (antidepressants caused a significant increase in my insomnia).

Often, insomniacs are so exceptionally sensitive to caffeine that they may be unable to sleep after one cup of tea or a chocolate bar in the afternoon. One study showed that patients who had caffeine induced wakefulness cleared caffeine more slowly from their bodies. The concentration of caffeine in their blood was higher at midnight, eight hours after afternoon coffee, than it was in other people (I have noticed an increased sensitivity to caffeine).

During wakefulness, the brain is kept in an alert state by the interaction of two major systems of nerve cells. Nerve cells in the upper part of the pons and in the midbrain, which produce acetylcholine, send inputs to activate the thalamus (The thalamus is involved in FFI). When the thalamus is activated, it in turn activates the cerebral cortex and produces a waking EEG pattern. Another important wakefulness center is in the basal forebrain, whose neurons project directly to the cerebral cortex. In addition to acetylcholine, other neurotransmitters promote wakefulness, including norepinephrine, serotonin, histamine, and glutamate.

During REM sleep, the cholinergic nerve cells and the thalamus and cortex are in a condition similar to wakefulness, but the brain is not very responsive to external stimuli. The difference is in the activity of three sets of monoamine nerve cells: the brainstem nerve cells in the locus coeruleus that use the neurotransmitter norepinephrine; the dorsal and median raphe groups that contain serotonin; and, in the hypothalamus, the tuberomammillary cell group that uses histamine. These monamine neurons fire most rapidly during wakefulness, but they slow down during slow wave sleep and stop during REM sleep. These monamine neurons act to suppress the occurrence of REM sleep.

The brainstem cell group that control arousal from sleep are, in turn, influenced by two groups of nerve cells in the hypothalamus, part of the brain that controls basic body cycles. One group of nerve cells, in the ventrolateral preoptic nucleus, contain the inhibitory neurotransmitter galanin and GABA. When the ventrolateral preoptic neurons fire, they are thought to turn off the arousal system, causing sleep. Damage to the ventrolateral preoptic nucleus produces irreversible insomnia. The ventrolateral proptic nucleus (VLPO) is a group of neurons in the hypothalamus. They are primarily active during non- rapid eye movement sleep, and inhibit other neurons that are involved in wakefulness. The VLPO neurons release the inhibitory neurotransmitters galanin and GABA to inhibit the monaminergic cell group in the locuse coeruleus, the raphe nucleus, and the tuberomammillar nucleus. VLPO is inhibited by the arousal transmitter noradrenaline and acetylcholine.

Published in Neurobiol. Learn Mem. 2009 Oct; 92(3): 429-38, entitled, "Impairment of memory consoldition by galanin correlates with in vivo inhibition of both LTP and CREB phosphorylation." Dr. Kinney and team found, changes in the state of CREB phosphorylation and in LTP in the hippocampus have been associated with learning and memory. Here we show that galanin, the neuropathies released in the hippocampus formation from cholinergic and noradrenergic fibers, that has been shown to produce impairment to memory consolidation in the Morris water maze task inhibits both LTP and CREB phosphorylation in the rat hippocampus in vivo. While there are many transmitters regulation CREB phosphorylation none has been shown to suppress behaviorally induced hippocampus CREB phosphorylation as potently as galanin.

In the paper "Neurotransmitters and Sleep," by Richard Hall, 1998, found on the internet, states the neurotransmitter that plays the largest role in sleep is acetylcholine (Ach). The Ach neurons that are most important in the sleep process have cell bodies in the Pons and the Basal Forebrain. Laboratory animals that have lesions to brain areas that contain Ach cell bodies decrease cortical arousal and desynchrony, and stimulation of these areas has opposite effect. Also, sleep and thermoregulation are strongly tied together. The basal forebrain area forms an important sleep and thermoregulation circuit with two nuclei in the hypothalamus, the anterior hypothalamus and Preoptic area. These three structures and the connections among them constitute the POAH. POAH nerve firing increase during sleep and in response to an increase

in body temperature. It appears that REM sleep initiation begins in the Ach neurons located in the pons, in one particular area called the Peribrachial Area. In one sense, the Ach neurons in this area of the brain are "REM headquarter."

A second group of nerve cells in the **lateral hypothalamus** influences and suppresses REM sleep. They contain the neurotransmitter orexin, which provides an excitatory signal to the arousal system, particularly to the monoamine neurons. In experiments in which the gene for the neurotransmitter orexin was experimentally removed in mice, the animals became narcoleptic. Similarly, in two dog species with naturally occurring narcolepsy, an abnormality was discovered in the gene for the type 2 orexin receptor. Recent studies show that in humans with narcolepsy, the orexin levels in the brain and spinal fluid are abnormally low. Thus, orexin appears to play a critical role in activating the monoamine system and in preventing abnormal transitions, particularly into REM sleep.

Two main signal control our need for sleep and its circuitry. First, there is homeostasis, or the body's need to seek a natural equilibrium of rest and sleep followed by wakefulness. Several mechanisms for the signal of accumulating sleep have been suggested. There is evidence that a chemical called adenosine, which is linked to brain energy depletion, accumulated in the brain during prolonged wakefulness and that it may drive sleep homeostasis. Interestingly, the drug caffeine, which is widely used to prevent sleepiness, acts as an adenosine blocker.

The other major influence on sleep cycles is the body's circadian clock, the suprachiasmatic nucleus. This small group of nerve cells in the **hypothalamus** contains clock genes, which go through a biochemical cycle of about 24 hour, setting the pace for daily cycles of activity, sleep, hormones, and other bodily functions. The suprachiasmatic nucleus also receives input directly from the retina, and the clock can be reset by light, so that it remains linked to the outside world's day night cycle. The suprachiasmatic nucleus provides signals to the brain areas regulation sleep and arousal.

Cheyne - Stokes respiration consists of a period of cessation of breathing (apnea) lasting 10 to 60 seconds, followed by gradually increasing depth and frequency of respirations. In her book, "Understanding Pathophysiology," by Sue Huether and Kathryn McCantes. They state Cheyne-Stockes Respiration can result from a condition that slow the blood to the brainstem. Slowing of blood flow to brainstem can produce Cheyne - Stokes respiration because it is mainly the brainstem that control breathing.

Prior to developing LD, and for most of my adult life, since the age of puberty, I have slept 8 hours only a handful of times. Before the age of puberty I slept normally. After puberty, I averaged 4 hours of sleep per night, sometimes more or less. Some people can survive on only 4 hours of sleep, but I have noticed I need more for me to function. During the 4 hours of sleep, 2 hours are mostly spent in a transit sleep. Then for the rest of the night I am tossing and turning, in and out of sleep. I am extremely susceptible to any noise that occurs during the night and wake easily. I have tried every technique imaginable to get a good night's sleep. All prescription sleep aids are mostly stimulants and prevent me from sleeping. Also any type of strenuous physical work over a long period of time causes a stimulator effect and increase the effects of my insomnia (especially if I drink allot of water on a hot day). To make up for lack of sleep during the night, I am able to nap during the day and sleep more on the weekends. When I contracted LD my ability to nap during the day has completely vanished. Because of my debilitating insomnia I function at the eighth grade level most of the day, which only adds to my hyperhidrosis. Not being able to function only increases the level of stress throughout the day. Not being able to function properly during the work day leads to mistakes and the impossibility of further advancement. It is another negative feedback loop. I have also noticed I need the TV to fall asleep at night. I have noticed when I am not able to sleep, I notice an increase in body temperature, and I feel hot. When I consume some types of food, after about an hour I notice body temperature drop and feel cool and sleepy. It seems my insomnia is a result of an inflammatory response, causes by a substance penetrating the intestinal wall and making its way to the brain resulting in inflammation, and my disorder.

I would describe my sleep condition as Nonrestorative Sleep (prior to LD). Throughout the night I am both asleep and awake at the same time. According to Dr. Moldofsky from the Clark Institute in Toronto studied a group of patients suffering from **Fibrositis** and found that most of them showed this intrusion of alpha (waking) waves into NREM sleep. He called it Nonrestorative sleep, and speculated that such patients do sleep, but get very little benefit from sleeping.

Psoriasis. Psoriasis is a chronic autoimmune disease that appears on the skin. It occurs when the immune system sends out faulty signal that speed up the growth cycle of skin cells. Various environmental factors aggravate psoriasis, such as stress. Abnormalities in several signaling pathway and

in the expression and/or activation of different transcription factors in psoriatic keratinocytes have been hypothesized in the path physiology of psoriasis. The mitogen activated protein kinase (MAPK) cascades are among the best characterized of intracellular signaling pathways, and they play an important roles in cell proliferation, differentiation, gene expression, and inflammation. Using immunohistochemistry and western blot in lesional psoriatic skin and normal skin, the immunoblot analysis demonstrated that activation of extra cellular signal regulated kinases (ERKs) and p38 mitogen activated protein kinase (p38 MAPK) increased in the lesional psoriasis. In addition, a significant increase in p-MEK (the upstream activator of ERK), and pCREB (downstream transcription factor of active ERK) was found in the experiment. The immunohistochemical study showed that the levels of phosphorylated ERK½ and p38 MARK were enhanced in lesional psoriatic skin compared to controls. Phosphorylated ERK½ and p38 exhibited clear nuclear localization throughout the epidermal part of lesional psoriatic skin. These finding suggested that ERK½ and p38 pathways were involved in the patho-physiology of psoriasis (69). In peripheral blood mononuclear (PBMCs) derived from patients with rheumatoid arthritis (RA), psoriasis and Crohn's disease compared with PBMCs from healthy subjects scientist found an up regulation of nuclear factor kappa (NF-KappaB) and CREB in the Gi protein associated A(3) adenosine receptor (A(3)AR) gene promoter. Up regulation of NF-KappaB and CREB was found in the PBMCs from patients with RA, psoriasis and Crohn's disease. The P13K-PKB/Akt signaling pathway, known to regulate both the NF-kappaB and CREB, was also unregulated in the patients' PBMCs. NF-KappaB and CREB are involved with the over expression of A (3) AR in patients with autoimmune inflammatory disease (70). In another study the activity of the p38 mitogen activated protein kinase (MAPKs) is increased in lesional psoriatic skin, supporting a possible role of these kinases in the pathogenesis of psoriasis. Increased focal activation of the downstream target mitogen and stress activated protein kinase 1 (MSK1) was demonstrated in psoriatic epidermis. The study demonstrated for the first time the expression of MSK2 in keratinocytes and increased MSK2 and CREB activation in lesional psoriatic skin. This indicates that the p38-MAPK/MSK1/MSK2 and CREB signaling pathway may play a role in the pathogenesis of psoriasis (71). In the Science Daily, August of 2009, scientist found a gene associated with psoriasis located HLA-CW*0602, SNP rs 10484554. However, many other genes play a role and have strong association with psoriasis. **Recently, psoriasis and rheumatoid arthritis suffers where associated with hyperhomocysteinemia.**

The epidermis is a very active site of lipid metabolism, and all peroxisome proliferator receptor (PPAR) and liver X receptor (LXR) isoforms are expressed in the epidermis. Activation of PPARalpha, beta/delta, or gamma or LXRs stimulates keratinocyte differentiation. Additionally, activation of these receptors also improves permeability barrier homeostasis by a number of mechanisms, including stimulating epidermal lipid synthesis, increasing lamellar body formation and secretion, and increasing the activity of enzymes required for the extra cellular processing of lipids in the stratum corneum, leading to the formation of lamellar membranes that mediate permeability barrier function. The stimulation of keratinocyte differentiation and permeability barrier formation also occurs during fetal development, resulting in accelerated epidermal development. PPAR and LXR activation regulates keratinocyte proliferation and apoptosis, and studies have shown that these receptors play a role in cutaneous carcinogenesis. Lastly, PPAR and LXR activation is anti-inflammatory, reducing inflammation in animal models of allergic and irritant contact dermatitis. Because of their broad profile of beneficial effects on skin homeostasis, PPAR and LXR have great potential to serve as drug targets for common skin diseases such as psoriasis, atopic dermatitis, and skin cancer (71). It is interesting there is clinical trials going on now (year 2010) for the drug Acotos, for the treatment of psoriasis. Actos has effect on PPAR gamma, and CREB has an effect on PPAR gamma.

Memory. The extra cellular signal regulated kinase (ERK/MAPK (mitogen activated protein kinase) cascade has been established as a potent regulator of gene transcription in long term memory formation, but the precise mechanisms of this regulation are poorly understood. ERK does not directly affect many of its nuclear targets, but rather must act through intermediary kinases. Mice lacking MSK1 show impaired Pavlovain fear conditioning and spatial learning, as well as a deficiency in histone phosphorylation and acetylating in the hippocampus after fear training. Hippocampal slices from MSK1 knock-out mice exhibit a deficiency, in both histone phosphorylation and acetylating after activation of the ERK pathway in vitro. MSK1 knock-out mice demonstrated a deficiency in CREB phosphorylation after fear training. CREB phosphorylation and histone acetylating represents parallel targets of MSK1 function. MSK1 is an important regulator in long term memory (73). Studies have shown that calcium/calmodulin-dependent protein kinase IV (CaMKIV is a serine/threonine kinase) functions as a positive regulator for memory

formation and that age related memory deficits are the result of dysfunctional signaling pathways mediated by CREB, the downstream transcription factor of CaMKIV. In transgenic mouse up regulation of CaMKIV led to an increase in learning induced CREB activity, increased learning related hippocampal potentiation, and enhanced consolidation of contextual fear and social memories (74).

Depression. The relationship between CREB and depressive behaviors is another good illustration of how the consequences of elevated CREB activity can differ throughout the brain. Depending on the brain region under study, elevated CREB function can either reduce or produced depressive like behaviors in laboratory animals. In the hippocampus, CREB appears to be a crucial mediator of antidepressant effects. A wide variety of standard antidepressant treatment, example noradrenaline reuptake inhibitors, SSRI's and electroconvulsive therapy, increase CREB activity within the hippocampus. Direct elevation of CREB protein levels using virus mediated gene transfer has antidepressant like effects in rodents (75). CREB regulates many genes involved the pathophysiology of depression. Increased CREB levels were found in the brain of antidepressant treated rats and decreased protein and mRNA expression of CREB was reported in the postmortem brain of depressed suicide victims. In major depressive patients (MDD) they found CRE-DNA binding activity and CREB protein expression were significantly decreased in the neutrophils of drug free MDD patients compared with normal subjects (76).

Published in Psychiatry Res., dated May 20, 2010, Dr. Pandey at the Department of Psychiatry, University of Illinois at Chicago found CREB protein regulates the expression of many genes involved in the path physiology of depression. Increased CREB levels were found in the brain of antidepressant-treated rats and decreased protein and mRNA expression of CREB was reported in the postmortem brain of depressed suicide victims. They determined CREB protein expression, using Western blot technique, and CRE-DNA binding, using gel shift assay, in neutrophils obtained from 22 drug free patients with major depressive disorder (MDD) and 23 normal control subjects. They found that the CRE-DNA binding activity and CREB protein expression were significantly decreased in the neutrophils of drug free MDD patients compared with normal controlled subjects. Their findings suggest that CREB may play an important role in the pathophysiology of depression and that it may be an important target for the therapeutic action of antidepressant drugs. Neutrophil CREB levels may also serve as a useful biomarker for patients with MDD.

Published in the International Journal of Neuropsychopharmacolgy, 2011, Jan. 12:1-12 (Epub ahead of print), entitled "Antidepressants elevate GDNF expression and release from C6 glioma cells in a B-arrestin1-dependent, CREB interactive pathway." Dr. Golan and team found the gilial cell line derived neurotrphic factor (GDNF), essential for neuronal survival, plasticity and development, has been implicated in the mechanism of action of antidepressant drugs (AD). Chronic AD treatment significantly increased CREB phosphorylation without altering the level of **total CREB** in the nuclear fraction of the cells (this might explain why Prozac increased my sweating substantially under my under arm, but it did improve, slightly, my cranial hyperhidrosis). Treatment with AD significantly increased B-arrestin1/CREB interaction. AD treatment generates a transcription complex involving CREB essential for GDNF expression and release, thus enhancing GDNF's neuroprotective action that promotes cellular survival and plasticity when the survival and function of neurons is compromised as occurs in major depression.

Italian scientist investigated the potential association of a set of single nucleotide polymorphisms (SNPs) in CREB1 in major depressed (MD) patients. 190 MD patients treated with antidepressants for 4 weeks were genotyped for 5 CREB1 SNPs (rs2709376, rs2253206, rs7569963, rs7594560, and rs4675690. An allele of rs7569963 as well as rs2253206-rs7569963 A-A and rs7569963-rs4675690 A-C haplotypes were associated with the status of treatment resistance. Additionally, rs756993 GG genotype was positively associated with remission (77).

The CREB gene has been located by Dr. Zubenko, at the University of Pittsburg, (9) at 15cM region of chromosome 2q33-35 flanked by D2S2312 and D2S2208 for families suffering with depressive disorders.

The CREB gene is located on chromosomes 2 and 16 which are involved in learning and memory. CREB gene located at 16p13.3, located on short area of chromosome 16 at position 13.3. CREB1 located at 2q34-2q33.3.

P53. The transcriptional activity of p53 is regulated by a cascade of posttranslational modifications. Although acetylating of p53 by CREB-binding protein (CBP)/p300 is known to be indispensable for p53 activation, the role of phosphorylation, and in particular multisided phosphorylation, in activation of CBP/p300-dependent p53 transcriptional pathways remain unclear. We investigated the role of single site and multiple site phosphorylation of the p53 Tran activation domain in mediating its interaction with CBP and with ubiquity ligase MDM2. In contrast, binding to CBP is modulated by the extent of p53

phosphorylation; addition of successive phosphoryl groups enhance the affinity for the TAZ1, TAZ2, and KIX domains of CBP in an additive manner. Activation of p53-dependent transcriptional pathways requires that p53 compete with numerous cellular transcription factors for binding to limiting amounts of CBP/p300. Multisite phosphorylation represents a mechanism for a graded p53 response, with each successive phosphorylation event resulting in increasingly efficient recruitment of CBP/p300 to p53-regulated transcriptional programs, in the face of competition from cellular transcription factors. Multisite phosphorylation thus acts as a rheostat to enhance binding to CBP/p300 and provides a plausible mechanistic explanation for the gradually increasing p53 response observed prolonged or severe genotoxic stress (78). Gene p53 is located on short arm of chromosome 17 (17p13.1).

Lyme Disease (LD). The bacteria that is associated with LD is Borrelia Burgdorferi (Bb). Lyme spirochetes are good at altering their structure to evade the host's immune system and can use the environment it is in to make alterations and adapt to any situation. The spirochetes have various subtypes and enter different sites, in different parts of the body, causing symptoms to vary from person to person. There are many co-infections associated with LD such as Babesiosis, Ehrlichiosis, Anaplasmosis, Barteonella, Mycoplasma and Chlamydia Pneumonia.

Published in the Journal of Applied Toxicology, and released on the internet. Found mast cells are key players in allergy, asthma and cancer and are important immune defense cells in the body, charged with fighting parasitic infections. They contain and release histamine and many other inflammatory mediators, which are needed for fighting parasites. The Gosse lab data suggest that **arsenic may inhibit** the ability of humans to fight of parasitic disease.

Many microorganisms (bacteria, fungi and yeasts) and animals are now known to biomethylate arsenic, forming both volatile and nonvolatile compounds, stated in Microbiol Mol. Biol. Rev. 2002 June, 66(2); 250-271.

Information from the internet, on LD, reveled in recent studies in both acute and antibiotic refractory, or chronic LD have shown a distinct pro-inflammatory immune process. This pro-inflammatory process is a cell mediated immunity and results in Th1 up regulation. These studies have shown a significant decrease in cytokine output of interleukin-10 (IL-10), and up regulation of Interlekin-6 (IL-6), Interleukin-12 (IL-12) and IFN-gamma and disregulation in TNF-alpha predominantly. These studies suggest that the host immune response to infection results in increased levels of IFN-gamma in the serum and lesions of LD patients that correlate with greater severity of disease. IFN-gamma alters gene expression by endothelia exposed to Bb in a manner that promotes recruitment of T cell and suppresses that of Neutrophils. Studies also suggest Suppressors of Cytokine Signaling (SOCS) proteins are induced by cytokines, and T cell receptor can down regulate cytokine and T cell signaling in macrophages. It is hypothesized that SOCS are induced by IL-10 and Bb and its lipoproteins in macrophages, and that SOCS may mediate the inhibition of IL-10 by concomitantly elicited cytokines. IL-10 is generally regarded as an anti-inflammatory cytokine, since it acts on a variety of cell types to suppress production of proinflammatory mediators. Researchers are also beginning to identify **microglia** as a previously unappreciated source of inflammatory mediator production following infection with Bb. Such production may play an important role during development of cognitive disorders in Lyme neuroborreliosis. This effect is associated with induction of nuclear factor-kappa B (NF-KB) by Borrelia. Disregulated production of pro-inflammatory cytokines such as IL-6 and TNF-alpha can lead to neuronal damage in Borrelia infected patients. IL-6 and TNF-alpha cytokines produce fatigue and malaise, two of the more prominent symptoms experienced by patients with chronic LD. IL-6 is also significantly indicated in cognitive impairment.

A developing hypothesis is that the chronic secretion of stress hormones as a result of Borrelia infection may reduce the effect of neurotransmitters, or other receptors in the brain by cell-mediated pro-inflammatory pathways, thereby leading to the disregulation of neurohormones, specifically glucocorticoids and catecholamine's, the major stress hormones. This process is mediated via the HPA adrenal axis. Additionally, Tryptophan, a precursor to serotonin appears to be reduced within the CNS in a number of infectious diseases that affect the brain, including LD. Researchers are investigating if this neurohormone secretion is the cause of neuro-psychiatric disorders developing in some patients with borreliosis.

New research has also found that chronic Lyme patients have higher amounts of Borrelia specific forkhead box P3 (FoxP3) than healthy controls, indicating that regulatory T cells might also play a role, by immunosuppressant, in the development of chronic LD. FoxP3 are a specific marker of regulatory T cells. The signaling pathway P38 mitogen activated protein kinases (p38 MAP kinase) has also been identified as promoting expression of proinflammatory cytokines from Borrelia. The culmination of these new and

ongoing immunological studies suggest this cell mediated immune disruption in the Lyme patient amplifies the inflammatory process, often rendering it chronic and self-perpetuating, regardless of whether the Borrelia bacterium is still present in the host, or in the absence of the inciting pathogen in an autoimmune pattern. This interpretation must however be considered against the evidence (above) for persistence of the spore form of Borrelia in human hosts, and the tendency for relapses to occur after antibiotics are continued. It is possible that whereas some chronic Lyme patients retain actual population of live spirochetes, others have symptoms brought only by an inflammatory or auto-immune reaction.

Some researchers contend Lyme is driven by chronic infection and recommend patients be treated with antibiotics for the long term. Other support the hypothesis that the disease is the result of autoimmune T cell activation that occurs subsequent to the initial infection or after the infection has cleared. Others hypothesis that LD is not just a bacterial infection, but hybrid bacterial virus bug.

In Experimental Neurology, Vol. 217, Issue 1, pp177-183, researchers found that when human microglia, or human monocytic THP-1 cells, were exposed in vitro to the **proton pump inhibitors**, their secretions became less toxic toward human neuroblastoma cells. In addition, they found that these drugs acted synergistically with ibuprofen. To confirm that the proton pump inhibitors were acting to inhibit inflammation, they found that lansoprazole and omeprazole reduced the secretion from THP-1 cells of the inflammatory cytokine tumor necrosis factor alpha (this might explain Tagment unusual effect on me while I was still suffering from undiagnosed LD).

In the journal Brain, 2005 June; 128(Pt 6):1442-53, researches theorized that the drug Actos could be used to reduce inflammatory markers in Alzheimer's patients. They discovered in mice that oral treatment with Actos resulted in a reduction in the number of activated microglia and reactive astrocytes in the hippocampus and cortex. Drug treatment reduced the expression of the proinflammatory enzymes cyclooxygenase 2 (COX2) and inducible nitric oxide syntheses (iNOS). Actos also decreased beta-secretase-1 (BACE1) mRNA and protein levels (this might explain my positive result with Actos).

In the Journal of Biological Chemistry, May 2006, 281, 14971-14981, the researches state that the microglia are considered as CNS resident professional macrophages that function as the principal immune effector cells of the CNS responding to any pathological event. Activation of microglia has been implicated in the pathogenesis of a variety of neurodegenerative diseases, such as Alzheimer, HIV associated dementia, stroke and MS. It has been found that activated microglia accumulate at sites of injury or plaques in neurodegenerative CNS. Although activated microglia scavenge dead cells from the CNS and secrete different neurotrophic factors for neuronal survival. It is believed that severe activation causes various autoimmune responses leading to neuronal death and brain injury. During severe activation microglia not only secrete various **neurotoxin** molecules but also express different proteins and surface markers. Among the different surface markers, CD11b. CD11b acts as a binding protein for intracellular cell adhesion molecule-1 and complement C3bi. It is reported that in various neuroinflammatory diseases, the increased CD11b expression corresponds to the severity of imbroglio activation. Because activated microglia also express inducible nitric oxide synthase (iNOS) to produce an excessive amount of NO (excessive amounts found in hyperhidrosis patients), a molecule implicated virtually in all reported neurodegenerative and neuroinflammatory conditions. It is reported that NO is instrumental in increasing the expression of CD11b in microglia. Different inducers of NO production such as LPS, IFN-y, IL-1B, HIV-1 gp120, and poly(IC) stimulated imbroglio expression of CD11b via NO. Furthermore, we also demonstrate that NO employed the guanylate cyclase (GC)-cGMP-cGMP activated protein kinase (PKG)-cAMP response element-binding protein (CREB) pathway to up regulate the expression of CD11b in microglia.

Microgila are normally really good cells to have, according to Dr. Jarred Younger, Stanford University School of Medicine. He also states, "**that microgila are our brain's immune system cells**, and when they detect a virus or something they become activated, and they produce a number of chemicals that help fight off the infection, but they also produce chemicals that make us feel sick." Younger hypothesis the microgila may be switched on, and stay on, even when there's no infection as with patients suffering from fibromyalgia.

In Neuroscience Letters, Volume 384, Issue 1-2, 12 August 2005, pages 112-116, Dr. Ramesh writes about how Lyme borreliosis is an infectious disease that may cause local inflammation in numerous organs. Lyme neuroborreliosis of the central nervous system also has inflammatory component. Dysregulation production of pro-inflammatory cytokines such as IL-6 and TNF-alpha can lead to neuronal damage. Mitogen-activated protein kinases (MAPK) play a key role in the regulation of neuronal development, growth, and survival, as well as the of pro-inflammatory cytokine production. Lipoproteins are key

inflammatory molecule type of Borrelia Burgdorferi, the spirochete that causes LD, and we had previously shown that lipoprotein-induced TNF-alpha production in astrocytes caused astrocyte apoptosis, and IL-6 enhanced proliferation of these cells. Lipoproteins readily activated p38 and Erk ½ MAPK, thus enlisting these pathways among the kinase pathways that spirochetes may address as they invade the central nervous system. We also investigated whether specific inhibition of p38 and Erk ½ MAPK would inhibit TNF-alpha and IL-6 production and thus astrocyte apoptosis, and proliferation, respectively. Lipoprotein stimulated IL-6 production was unaffected by the MAPK inhibitors. In contrast, inhibition of both p38 and Erk½ significantly diminished TNF-alpha production, and totally abrogated production of this cytokine when both MAPK pathways were inhibited simultaneously. MAPK inhibition thus may be considered as a strategy to control inflammation and apoptosis in Lyme neuroborreliosis.

Dr. Fallon, head of the Lyme Disease Research Center, Columbia University, stated patients with persistent neurological symptoms after treatment for neurological LD, controlled MRI studies have not demonstrated an increased burden of white matter hyper intensities, indicating that structural damage is not the explanation for persistent symptoms. Functional imaging studies, however, of patients with later stage neurological LD using either PET or SPECT scans have consistently demonstrated abnormalities suggestive of impaired blood flow and or metabolism, which may improve after antibiotic treatment. Patients with Lyme encephalopathy had a diminished ability to increase cerebral blood flow in response to Hypercapnic challenge compared to controls, a finding that would suggest vascular compromise (as perhaps from inflammation) as part of the disease process. The precise cause of these objective vascular and metabolic deficits however is unclear. While some of these patients do respond to repeated antibiotic therapy, the antibiotic responsive itself need not indicate persistent infection as antibiotics are also known to have roles in modulating glutamate and reducing inflammation.

Dr. Fallon found that animal models of neurologic LD raises the question whether activated glial cells and their soluble products are responsible for persistent brain dysfunction, such as deficits in short term memory, verbal fluency, and processing speed. To explore the possibility that **miroglia are activated in** CNS disease, it is now possible to conduct brain PET imaging studies using radioactive ligands that target microglia. **The translocation protein (TSPO)** is expressed primarily on microglia when activated in CNS injury. In vivo imaging can document the expression of TSPO using radio labeled ligands such as PK11195 which is the best studied of the tracers. PET studies using PK11195 have been conducted for a vast range of CNS diseases, including Rasmussen's encephalitis, multiple sclerosis, neurodegenerative disease, and infectious diseases (HIV, Herpes encephalitis), with many studies showing increased retention of PK11195, suggesting Microglial activation. PK11195 however has limitations, chief of which is a low binding signal and poor permeability of the non-compromised blood brain barrier resulting in poor sensitivity. Other TSPO radioligands are now being studied, with early reports for some suggesting higher binding affinity to TSPO. The application of these PET radioligands in future controlled studies to patients with both acute and chronic CNS LD holds the promise of determining whether activated microglia are present at different stages of neurlogic LD and whether TSPO binding can serve as a biomarker of ongoing disease activity and treatment response.

Alzheimer's Disease. Alzheimer's disease is characterized by the accumulation of neuritic plaques that contain dead and dying neurons and their processes, **inflammatory activated microglia** and B-amyloid peptides AB1-10 and AB 1-42. The disease is accompanied by brain inflammation, characterized by increased cytokine levels and increased numbers of activated microglia. Epidemiological studies have indicated that non-steroidal anti-inflammatory drugs prevent or delay the onset of Alzheimer's, suggesting that brain inflammation contributes to disease progression prior to clinical symptoms. B-Amyloid and cytokines cause inflammatory activation or gila, and **inflammatory-activated microglia** are consistently found in the neuritic plaques of Alzheimer's patients. B-Amyloid, cytokines and/or bacteria-activated microglia potently kill co-cultured neurons, and the ultimate means by which neurons are killed in a wide range of brain pathologies may be inflammatory neurodegeneration mediated by activated microglia. Microglia have a specific NADPH oxidase known as PHOX (phagocytic oxidase), consisting of subunits gp91 (NOX2), p22, p47, p67, p40 and Rac. Normally in resting microglia this oxidase is relatively inactive and unassembled, but when activated by B-amyloid, **bacteria** and/or cytokines, the oxidase assembles at the plasma membrane, and produce superoxide that is released extracellular or into phagosomes at a high rate. The superoxide either dismutates to H_2O_2 or reacts with NO to produce cytotoxic peroxynitrite. We and others believe that NADPH oxidase activation is the key event converting resting microglia to activated, proliferating, cytotoxic microglia and therefore, that blocking oxidase activation may block inflammatory neurodegeneration. We have recently found that proliferation of

microglia is dependent on H2O2 from PHOX, that cytokines, arachidonate and ATP stimulate imbroglio proliferation via stimulating H2O2 production from PHOX; and that inhibiting PHOX prevents this. We also found that imbroglio PHOX and ROS and nitrogen species are key mediators of inflammatory killing of neurons. Others have shown that activation of H2O2 production form PHOX is a required step for inflammatory activation of microglia induced by LPS. In conclusion, the results indicated that AB1-40 induced imbroglio proliferation is mediated both by imbroglio release of TNF-alpha and production of H2O2 from NADPH oxidase. This suggest that TNF-alpha and NADPH oxidase, and its products, are potential targets to prevent AB-induced inflammatory neurodegeneration (79).

A live discussion at the University of Illinois, Chicago, dated December 16, 2002 with Dr. Elena Galea and Dr. Douglas Feinstein about how PPAR agonist and Advil reduces inflammation. Actos can be used to treat neurological diseases such as Alzheimer's. Feinstein presented data showing PPAR agonists reduce brain's inflammatory response to injection of aggregated amyloidB42 (AB42). In this model, previous ablation of the Locus Coeruleus, a noradrenergic nucleus that is the major source of noradrenaline in the brain, leads to robust cortical inflammatory response to AB42. Loss of the LC occurs in the majority of Alzheimer's patients, leading Feinstein to propose that reduced **noradrenaline levels** might exacerbate the inflammatory responses to AB in Alzheimer's disease. AB injection induced robust IL-1B and iNOS expression, and these responses were reduced by co injection of ibuprofen and Actos. Oral administered PPAR agonist can reduce brain glia inflammation. Also, Actos has been found to cross the blood brain barrier.

Prostate Cancer. At the Brady Urological Institute, John Hopkins, published in winter of 2008, Vol. IV. Dr. Casero showed that inflammation plays a key role in the development of prostate cancer. Inflammation causes oxidative damage, harm to DNA, which can cause one or more genes to mutate and this, in turn, can lead to cancer. One substance known to cause oxidative damage is H2O2, which is produced when there is inflammation. It doesn't take much, very tiny amounts, even just one molecule's worth, can cause harm. What, in inflammation, causes H2O2 to be made? This can happen when an enzyme called spermine oxidase mixes with oxygen with spermine, a substance found in high concentrations in the prostate. Casero found that when there is inflammation in the stomach (caused by bacterial infection with H. pylori) spermine oxidase makes H2O2, and damages DNA. Casero suspected that this also happens in the prostate, which has the highest concentration of spermine of any human tissue. Casero has found that inflammation, inflammatory cytokines, causes more spermine oxidase to be made. "Our data indicate that increased spermine oxidase is associated with prostate cancer, "he stated. "As the product of spermine oxidase is H2O2, we suspect that this can lead to greater DNA damage, and ultimately, to the initiation and progression of prostate cancer." This might explain the funny looking stain that is present on all of my underwear (looks like dried blood). Maybe this stain on my underwear is H2O2 ????????

Conclusion

The medical establishment should consider the more toxic forms of heavy metals as the possible trigger mechanism behind hyperhidrosis. Additional research in this areas is needed, but without conclusive diagnostic testing it is only a theory. Hyperhidrosis is simple an irritation of the pituitary gland caused by a more toxic form of the heavy metal parent compound.

If scientist are going to conduct any diagnostic lab procedures in the future, the testing procedure should be performed in a certain way. The test subjects should be separated based upon the area of the hyperhidrosis that is effected, palmer, planter, axillary, axillary and planter, all over, etc. The testing procedure for subjects suffering the effects of hyperhidrosis should be tested before, during and after that person's interpretation of a stressful event. The lab results will have false readings for subjects suffering from hyperhidrosis it the testing procedures are not followed in this manner. The scientist will discover that before, during and after a stressful event CREB will not be activated and maintained throughout the testing procedure. The testing procedure should be conducted under the patient's interpretation of a stressful event, usually 1 to 2 hour period. Scientist will discover that a build-up of the HPA axis will occur slowly over this period of time. At some point, the adrenal gland will become overextended and

reach a crescendo. At that point, the adrenal glands will fluctuate continuously, causing variation of norepinephrine, epinephrine, and catecholamine's as the HPA axis becomes exhausted trying to activate CREB.

Only a handful of times in my life I experienced the wonderful effects of not suffering from my disorder, which has motivated me for many years to find a cure. At this moment I am 46 years old and I can honestly say my entire life has been dictated by hyperhidrosis and insomnia, preventing me from enjoying life to the fullest. When my disorder first appeared hyperhidrosis was more of a debilitating factor compared to the insomnia, but as I have gotten older, and been afflicted with LD, the insomnia has overwhelmed my life in the last few years. All I can do is pray to God for a miracle, I hope this paper will bring peace of mind and some knowledge for the sufferers of hyperhidrosis.

References

(1) Arsenic species, AS3MT amount, and AS3MT gen expression in different brain regions of mouse exposed to arsenite. Enviromental Research 110 (2010) 428-434. Petrosyan, Gonsebatt, Del Razo,
(2) Individual variations in inorganic arsenic metabolism associated with AS3MT genetic polymorphisms. International Journal of Molecular Science (2011) Vol. 12 Issue 4, 2351-2382.
(3) Generation of thioarsenicals is dependent on the enteroheptic circulation in rats. Metallomics 2011 Oct,3(10):1064-73. Wany, Bu, Hao.
(4) Arsenic exposure to low to moderate levels and skin lesions, arsenic metabolism, neurological functions, and biomarkers for respiratory and cardiovascular disease: Review of recent finding form the Health Effects of Arsenic Longitudianl Study (HEAL) in Bangladesh. Toxicology and Applied Pharmacology. 239, (2009) 184-192. Chen, Ahsan, Gamble.
(5) Genetic polymorphisms influencing arsenic metabolism: evidence from Argentina. Environmental Health Perspectives. Apr. 1 2007. Engstrom, Schlawicke, Karin.
(6) Individual variations in inorganic arsenic metabolism associated with AS3MT genetic polymorphisms. International journal of molecular sciences (2011) vol. 12 issue 4. Pages 2351-2382. Agusa,Fujihara, Iwata.
(7) The MRP2/cMOAT transporter and arsneic glutathione complex formation are required for billiary excretion of arsenic. Journal of Biological Chemistry. Oct. 2000, 275, 33404-33408.
(8) The effects of arsenic trioxide on brain monoamine metabbolism and locomotor activity of mice. Toxicology letters, 1990 vol 54, pg 345-353. Zhang, Saito, Ithoh.
(9) Effects of chronic exposure to sodium arsenite on hypothalamo-pituitary testicular activities in adult rats: possible an estrogenic mode of action. Reproduction Biol Endrocrinol. 2006, 4:9. Jana, Samanta.
(10) Chronic low level arsenic exposure causes gender specific alteration in locomotor activity, dopaminergic systems, and thioredoxin expression in mic. Toxicology and Applied Pharmacology 2009 vol 239, issue 2 pages 169-177. Bardullas, Giordano, Carrizales.
(11) Moderate perinatal arsnic exposure alters neuroendocrine markers associated with depression and increases depressive like behaviors in adult mouse offspring. Neurotoxicology, 2008, july 29(4); 647-655. Martinez, Kolb, Bell.
(12) Lifetime consequences of combined maternal lead and stress. Basic Clin. Pharmacol Toxicol 2008. Feb 102(2):218-27.
(13) Arsenic, cadmium, lead, and Mercury in sweat:a systematic review. Journal of environmental and public health. Vol 2012. Sears, Kerr, Bray.
(14) Chelating ability of Sulbactomax drug in arsenic intoxication. African Journal of Biochemistry Research Vo. 5(10), pp307-314, Sep 2011. Dwivedi, Gupta, Kumar, Chaudhary.
(15) Polymorphisms in arsenic (+III oxidation state) methyltransferase (AS3MT) predict gene expression of AS3MT as well as arsenic metabolism. Enviromental health perspectives (2011) vol 119, issue2 p. 182-88. Engstrom, Vahter, Broberg.
(16) Population differences in the human arsenic (+3 oxidation state) methyltransferase (AS3MT) gene polymorphism detected by using genotyping method. Toxicol. Appl pharmacol 2007, Dec 15, 225(3);251-4.
(17) The association between two common mutations C677T and A1298C in human Methyleneteetrahdrofolate Reductase Gene and the risk for diabetic nephropathy in Type II diabetic patients. Journal of Nutrition. Oct 1, 2000 vol 130, p 2493-2497. Friedman, Raz, Wexler.
(18) Genetic variation in genes associated with arsenic metabolism: glutathione S-transferase omega 1-1 and purine nuclesoide phophorylas polymorphisms in Eurpoean and indigenous americans. Environ Health Perspect 2003 Aug;111(11):1421-7. Yu, Kalla, Vidrine.
(19). Protien oxidative damage in arsenic induced rat brain: influcend of dl-alpha Lipoic acid. Toxicol Lett. 2005 jan15:155(1)27-34. Samuel, Jayavelu.
(20) Protection effect of taurine on nitrosative stress in mice brain with chronic exposure to arsneic. J biomed Sci. 2010:17,published online. Ma, Sasoh, Piao.
(21) Alpa Lipoci Acid decrease arsenic in the brain. Arch Toxicol. 2005 Mar 79(3):140-6. Shila, Subathra.
(22) Hepatoprotective and neuroprotective activity of liposome quercetin in combating chronic arsenic induced oxidative damage in liver and brain of rats. Drug delivery. Issn; 1521-0464
(23) Protective effects of selenium, calcium, and magnesium against arsenic induced oxidative stress in male rats. Arh hig rada toksikol. 2010 jun1,61(2)153-9. Srivastava,flora.
(24) Folic acid supplementation lowers blood arsenic. Am J Clin Nutr. 2007. Oct:86(4);1202-1209.
(25) Consumption of folate related nutrients and metabolsim of arsenic in Bangladesh. Am J Clin Nutr. May 2007, vol85nos 5 1367-

1374. Heck, Chen, Ahsan.
(26) Neuroprotective efficacy of curcumin in arsenic induced cholinergic dysfuction in rats. Neurotoxicology 2011 Dec.32(6):760-8.
(27) Protective effect of arjunolic acid against arsenic induced oxidative stress in mouse brain. Journal of biochemical and molecular toxicology 2008, vol 22,issue 1, pages15-28. Sinha, Manna.
(28) Dietary intake and arsenic methylation in a US population. Environ Health Perpective 2005 Sep. 113(9);1153-1159. Steinmaus, Smith. Carrigan.
(29) Lee, Jantzie, Todd. Postresuscitation N-Acetylcysteine treatment reduces cerebral hydrogen peroxide in the hypoxic piglet brain. Intensive Care Medicine vol. 34, issue 1, Jan. 2009, 190-197.
(30) Ferreira. Changes in hippocampus gene expression by 7-nitroindazole in rats submitted to forced swimming stress. Gene Brain Behavior. 2011 Dec. 5. Doi 10, 1111j. 1601-183x. 2011.0757.
(31) Kasdallah-Grissa A, Mornagui B, Aouani E. Resveratrol, a red wine polyphenol, attenuates ethanol induced oxidative stress in rat liver. Life Sci. 2007 Feb 20, 80 (11): 1033-9.
(32) Fullerton, Ditelberg. Copper/zinc super oxide dismutse transgenic brain accumulates hydrogen peroxide after perinatal hypoxiz ischemia. Ann Neurol. 1998 Sep;44(3):357-64.
(33) Nindl G. Hydrogen Peroxide-From Oxidative stressor to redox regulator. Cellscience Review Vol 1, No. 2 Issn 1742-8310.
(34) Pacher, Beckman, Liaudet. Nitric Oxide and peroxynitrite in health and disease. Physiol Rev. 2007 Jan. 87(1):315-424.
(35) Brunson KL, Avishai-Eliner S, Hatalski CG, Baram TZ. Mol Psychiatry. 2001 Nov6(6):647-56.
(36) Morinobu Shigeru. Folia Pharmacologica Japonica. Vol 116:107-110.
(37) Boer U, Alejel T, Belmeshe S,Cierny I, Krause D, Knepel W, Flugge G. CRE/CREB driven up regulation of gene expression by chronic social stress in CRE Luciferase Transgenic Mice: reversal by antidepressant treatment. Plos One. 2007 May 9, 2:e431.
(38-39) Mamiya N. Fukushima H, Suzuki A, Matsuyama Z, Homma S, Frankland PW, Kida S. Brain region specific gene expression activation required for reconcolidation and extinction of contextual fear memory. J Neurosci 2009 jan 14:29(2):402-13.
(40) Sabben El, Hebert MA, Liu X, Nankova B, Serova L. Differnitial effects of stress on gene transcription factors in catecholaminergic systems. Ann NY Acad Sci. 2004, Dec:1032:130-40.
(41) Kwon MS, Seo YJ, Shim EJ, Choi SS, Lee JY, Suh HW. The effect of single or repeated restraint stress on several signal molecules in paraventricular nucleus, arcuate nucleus and locus coerculeus. Neuroscience 2006 Nov 3, 142(4):1281-92.
(42) Broek, Bradshaw, Szabadi. The effects of psychological stressor and raised ambient temperature on the pharmacological reponsiveness of human eccrine sweat glands: implications for sweat gland hyper-responsivenss in anxiety stats. Eur. J Clin Pharmacol (1984) 26:209-213.
(43) Maple, Bradshaw, Szabadi. Pharmacoogical responsivness of sweat glands in human maxillae. Brit. J Psychiat. (1982) 141, 154-161.
(44) Sato, Leidal. Morphology and development of an exocrine sweat gland in human maxillae. American Physiological Society 1987. R166-r180.
(45) Karaca S, Kulac M, Uz E, Mollaoglu H, Yilmaz HR. Erythrocyte oxidant/antioxidant status in essential hyperhidrosis. Mol Cell Biochem. 2006 Oct290(1-2):131-5. Epub 2006 May 23.
(46) Karaca S, Kulac M, Uze E, Barutcu I, Yilmaz HR. Is nitric oxide involved in the path physiology of essential Hyperhidrorsis? Int J Dermatol. 2007 Oct;46(10):1027-30.
(47) Thatcher GR, Bennett BM, Reynolds JN. No chimeras as therapeutic agents in Alzheimer's disease. Curr Alzheimer Res. 2006 Jul;3(3):237-45.
(48) Lee B, Cao R, Choi YS, Cho Hy, Rhee AD, Hah CK, Hoyt KR, Obretan K. The CREB/CRE transcriptional pathway: protection against oxidative stress-mediated neuronal cell death. J Neurochem. 2008 Dec. 20 (equb ahead of print).
(49) Patel. Norepinephrine and nitric oxide promote cell survival signaling in hippocampus neurons. Eur. J Pharmacol. 2010 May 10; 633 (1-3) 1-9.
(50) Xu H, Luo C, Richardson JS, Li XM. Recovery of hippocampus cell proliferation and BDNF levels, both of which are reduced by repeated restraint stress, is accelerated by chronic venlafxine. Pharmacogenomics J. 2004;4(5):322-31.
(51) Sarandol A, Sarandol E, Eker SS, Erdine S, Vatansever E, Kirli S. Major depressive disorder is accompanied with oxidative stress: short term anideprressant treatment does not alter oxidative an Antioxidative systems. Psychopharmacol 2007 Mar:22(2):67-73.
(52) Mona Johannessen, Marit Pedersen Delghandi, Ugo Moens. What turns CREB on? Cellular Signalling 16 (2004) 1211-1227
(53) Kurzen H, Schallreuter KU. Novel aspects in cutaneous biology or acetylcholine synthesis and acetylcholine receptors. Exp. Dermatol 2004: 13 suppl 4:27-30.
(54) Sato. Sweat secretion by human axillary Apoeccrine sweat gland in vitro. American Physiological Society 1983. R203-R208
(55) Sato. Pharmacological responsiveness of the my epithelium of the isolated human axillary aporince sweat gland. British Journal of Dermatology 1980 103, 235-243.
(56) Vaalasti, Tainio, Rechardt. Vasoactive Intestinal Polypeptide (VIP) like immunoreacivity in the nerves of human axillary sweat glands. The Journal of Investigative Dermatology. 85, 246-248, 1985
(57) Aronson PJ, Laorincz AL. Promotion of palmar sweating with oral Phosphatidylcholine. Acta Derm Venereal 1985,65(1):19-24
(58) Mbongo-Kama E, Harnosis F, Mennecier D, Leclercq E. MDR3 mutation associated with intrepid and gallbladder cholesterol cholelithiasis: an update. Ann Hepatol. 2007 Jul-Sep;6(3):143-9
(59) Smith AJ, Van Helvoort A, Van Meer G. MDR3 P-glycoprotein, a Phosphatidylcholine transposes, transport several Cytotoxic drugs and directly interacts with drugs as judged by interference with nucleotide trapping. J Biol Chem. 2000. Aug 4:275(31):23530-9
(60) VanBerge-Henegouwen GP. Relevance of heritary defects in lipid transport proteins for the pathogenesis of cholesterol gallsones disease. Scand J Gastroenterol Suppl. 2004;(241):60-9
(61) Smith AJ, Van Helvoort A, Van Meer G. MDR3 P-glycoprotein, a Phosphatidylcholine transposes, transport several Cytotoxic drugs and directly interacts with drugs as judged by interference with nucleotide trapping. J Biol Chem 200, Aug4;275(31):23530-9
(62) Houten, Watanabe, Auwerx. Endocrine function of bile acids. The EMBO Journal. March 2006 25, 1419-1425
(63) Lefebre, Cariou, Lien, Kuipers, Staels. Role of bile acids and bile acid receptors in metabolic regulation. Physiol. Rev. 2009. 89; 147-191
(64) Kyung M, Cantor R, Lange K, Ahns S. Palmer Hyerhidrosis: evidence of genetic transmission. J Vasc Surg, 2002,35:382-6

(65) Lifu Wang, Anne-Chritine Piquet, Karin Schmidt, Thierry Tordjmann, and Jean Francois Dufour. Activation of CREB by Tauroursodeoxycholic Acid protects cholangiocytes from apoptosis induced by mTOR inhibition. Hepatology, Vol 41, No. 6, 2005:1241-1251
(66) Gyurcsovics K, Bertok L. Pathophysilogy of psoriasis: coping endotoxins with bile acid therapy. Pathophysiology 2003 Dec,10(1) 57-61
(67) Itoh S, Kono M, Akimoto T. Psoriasis treated with urodenxycholic acid. Three case reports. Clin Exp Dermatol 2007 Jul;32(4):398-200
(68) Graves L, Hellman K, Veasey S, Blendy J, Pack A, Abel T. Genetic evidence for a role of CREB in sustained cortical arousal. Neurophysiol 90:1152-1159, 2003 April.
(69) Yu XJ, Li CY, Dai HY, Cai DX, Wnag KY, Xu YH. Expression and localization of the activated mitogen actived protien kanase in lesional psoriatic skin. Exp Mol Pathol 2007 Dec,83(3):413-8
(70) Ochaion A, Bar-Yehunda S, Cohen S, Barer F. The anti-inflammatory target A(3) adenosine receptor is over expressed in rheumatoid arthritis, psoriasis and Crohen's disease. Cell Immunol 2009, 258(2):115-22
(71) Funding AT, Johansen C, Kragballe K, Iversen L. Mitogen and stress activated protein kinase 2 and cyclic AMP reponse element binding protien are activated in lesional psoriatic epidermis. J Invest Dermatol 2007 Aug, 127(8):2012-9
(72) Schmuth M, Jiang YJ, Dubrac S, Elias PM, Feingold KR. Thematic review series: skin lipids. Peroxisome proliferator activated receptors and liver X receptors in epidermal biology. J Lipid Res 2008 Mar, 49(3):499-509
(73) Chwang WB, Arthur JS, Schumacher A, Sweatt JD. The nuclear Kinase mitogen and stress activated protein kinase 1 regulates hippocampus chromation remodeling in memory formation. J Neurosci. 2007 Nov 14,27(46):12732-42
(74) Fukushima H, Maeda R, Suzuki R. Upregulation of calcium/calmodulin-dependent protein kinase IV improves memory formatioin and rescues memory loss with aginig. J Neurosci 2008 Oct 1;28(40):9910-9
(75) Carlezon W, Duman R, Nestler E. The many faces of CREB, Trends in Neuroscience Vol 28, No. 8 August 2005, 436-445
(76) Ren X, Dwivedi Y, Mondal AC, Pandey GN. Cyclic AMP reponse element binding protein (CREB) in the entropies of depressed patients. Psychiatry Res 2010 May, (Epub ahead of print)
(77) Serriti A, Chiese A, Calati R, Massat I. A preliminary investigation of the influence of CREB1 gene on treatment resistance in major depression. J Affect Disord. 2010 Jul 17. (epub ahead of print)
(78) Lee CW, Ferreon JC, Ferreon AC, Arai M, Wright PE. Graded enhancedment of p53 binding to CREB-binding protien (CBP) by multisided phosphorylation. Proc. Natl Acad Sci USA. 2010 Nov 9, 107(45):19290-5. Equb 2010 Oct 20
(79) Jakabsone, Mander, Ticler, Sharpe, Brown. Fibrilliar beta-amyloid peptide ABI-40 activates imbroglio prolifferation via stimulating TNF-alpha release and H202 derived from NADPH oxidase: cell cultures study. Neuroinflammation 2006, 3:24