

## **Autoimmune Inflammatory disorders (The Flame Within) Prevention, Risk Factors, Diagnosis, Medical and Alternative Treatments.**

### **Preface**

This book is addressed to solve the personal, social and medical challenges facing the individuals, implications to the individuals suffering from the difficult to diagnose conditions are provided. Thousands of individuals with Chronic Fatigue and Fibromyalgia, Multiple Sclerosis, neuropathy and epilepsy can improve with immunomodulatory treatments.

Autoimmune diseases **have become the number one diseases process today**. Currently heart disease, diabetes, cancers, strokes are all fueled by autoimmune mechanisms. By a mechanism called molecular mimicry which is the basis of all of autoimmune diseases; a deceived immune system starts to attacks its own body cells, which it was supposed to protect.

Treatment of autoimmune diseases should be directed at the cause. We present our case against pathogens responsible for deceiving our immune system and causing autoimmune disease. Removing the causative organism has ended the era of deception, thousands of individuals have improved and couple of hundred reports has been published confirming what you will find in this book.

Majority of the diseases are triggered by know pathogens, gliadin a glycoprotein in gluten causes Celiac disease. It is necessary to remove these proteins to achieve a cure from autoimmune diseases they cause. We have included treatment guidelines which range from over the counter diet products to expensive infusions. Guidelines for treatment of Alzheimer's, arthritis, heart attacks, Fibromyalgia and Chronic Fatigue are provided.

Even the diagnosis of autoimmune disease has been simplified by observation of the disease cycle. Simple tests to confirm inflammatory disease and associated immune deficiency are provided. We hope to revolutionize the treatment of autoimmune diseases, by illuminating a step by step process to diagnose and treat the molecular basis.

Autoimmune conditions keep on growing daily so those diseases not addressed will be included in the upcoming edition."

Thanks

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### **Glossary**

**AIDS:** Acquired Immune Deficiency Syndrome. The AIDS virus invades the T4 helper/inducer lymphocytes and multiplies, causing a breakdown in the body's immune system, eventually leading to overwhelming infection and/or cancer, autoimmune diseases with death

**A.I.D.P.** Acute (sudden onset) Inflammatory Demyelinating Polyradiculoneuropathy

**A.I.O.N.** Anterior Ischemic Optic Neuropathy, loss of vision due to inflammation in posterior ciliary artery circulation in the optic nerve head.

**Anaerobic:** Of, relating to, or being activity in which the body incurs an oxygen debt (for example weight training or resistive exercises) and does not immediately burn off a lot of calories and fat.

**Anti-inflammatory:** Reducing inflammation by acting on body mechanisms, without directly acting on the cause of inflammation, e.g., glucocorticoids, aspirin.

**Autoantibodies:** Autoantibodies are Y shaped proteins that attack specific proteins or other substances found in specific tissues or organs of the body. They are created by the immune system when it fails to distinguish between "self" and "non-self." (They can be called the bad antibodies, e.g. "antinuclear antibody",).

**Autoimmune Disease:** One of a large group of diseases in which the immune system turns against the body's own cells, tissues and organs, leading to chronic and often deadly conditions.

**Autonomic failure** or dysautonomia develops when the small nerves controlling heart rate, blood pressure, bowel movements, and skin color and hair integrity get involved with disease. Individuals either have low blood pressure or high blood pressure, heart rate slow or fast.

**Axonal degeneration**, sometimes referred to as the "dying-back" phenomenon, results in axonal degeneration at the most distal extent of the axon. Axonal degenerative polyneuropathies are usually symmetric, and as the disorder progresses, the axons typically degenerate in a distal-to-proximal gradient. Axonal degeneration is the most common type of pathologic reaction in generalized polyneuropathies, and it is often attributed to a "metabolic" etiology.

**Carotenoids:** Carotenoids are a group of more than 700 compounds that produce the red, yellow, and orange colors found in many fruits and vegetables. Beta carotene (also called provitamin A) is the most widely studied carotenoid, but others are proving to be of great interest. Carotenoids are neither vitamins nor phytochemicals, but are proving to be very important for health.

**C.D.C.** Center of Disease Control in the U.S.A. which issues disease alerts.

**Cynocobalamine** Vitamin B12

**Bacteria:** Microscopic germs. Some bacteria are "harmful" and can cause disease, while other "friendly" bacteria protect the body from harmful invading organisms.

**Borrelia burgdorferi** a Spirochete which causes Lyme Disease has World Wide distribution. Symptoms of Lyme disease vary from person to person, and do not appear until 6–8 weeks after the tick bite, the infection is difficult to diagnose. Blood test used to detect levels of antibodies, immunoglobulin M (IgM) and immunoglobulin G (IgG) that develops against the *Borrelia burgdorferi*.

**Bronchitis:** Inflammation of the mucous membrane of the bronchial tubes, frequently accompanied by cough, hypersecretion of mucus, and expectoration of sputum. Acute bronchitis is usually caused by an infectious agent and of short duration. Chronic bronchitis, generally the result of smoking, may also be known as **Chronic Obstructive Pulmonary Disease (COPD)** or **Emphysema**.

**Cancer:** Refers to the various types of malignant neoplasms that contain cells growing out of control and invading adjacent tissues, which may metastasize to distant tissues.

**Candidiasis:** Infection of the skin with any species of candida, usually *Candida albicans*. The infection is usually localized to the skin, nails, mouth, vagina, bronchi, or lungs, but may invade the bloodstream. It is a common inhabitant of the GI tract. Growth is encouraged by a weakened immune system, or with the prolonged use of antibiotics. Vaginal **symptoms** include itching, pain when urinating, and vaginal discharge.

**Clarithromycin** or Biaxin is an antibiotic used to treat certain infections caused by bacteria, such as pneumonia; bronchitis; and ear, lung, sinus, stomach, skin, and throat infections. It also is used to prevent disseminated Mycobacterium avium complex (MAC) infection. Antibiotics will not work for colds, flu, or other viral infections.

**C.N.S:** Central Nervous System (Brain and spinal cord).

**Chronic:** Usually Chronic illness: Illness extending over a long period of time.

**Ciliary:** Often Ciliary activity: Activity of the eyelashes or any hairlike processes (cilia).

**Cold agglutinins:** are abnormal proteins in the blood. They act as antibodies, causing red blood cells to clump together and die prematurely — especially at temperatures colder than normal body temperature

**CRP:** C-REACTIVE PROTEIN a test used to measure autoimmune disease (0 is normal)

**C.T. scan;** Computed tomography scan makes pictures of the body by using x-rays and a computer.

**Cytokines:** Cytokines are chemical messengers that control immune responses. They are secreted by white blood cells, T cells, epithelial cells and some other body cells. There are at least 17 different kinds of interleukin and 3 classes of interferon called alpha, beta and gamma and various subsets. Interleukins and interferons are called "cytokines" and there are two general groupings, Th1 and Th2. Th1 (T-cell Helper type 1) promote cell-mediated immunity (CMI) while Th2 (T-cell Helper type 2) induce humoral immunity (antibodies).

**Demyelination** refers to focal loss of the **myelin** (outer nerve sheath) sheath with sparing of the axon (central fibers in the nerve). This reaction can be seen in focal mononeuropathies (single nerve injury) or generalized sensorimotor or predominantly motor neuropathies. Demyelination in the brain and spinal cord causes Multiple Sclerosis and in the peripheral nerves it causes (CIDP).

**D.I :** Diabetes Insipidus. Some people with diabetes insipidus have kidneys that don't concentrate urine very well (meaning their urine is more diluted). They have to urinate very often. People with diabetes insipidus are thirsty all the time

**Diabetes Mellitus:** A disease with increased blood glucose levels due to lack or ineffectiveness of insulin.

**E.A.U.:** experimental autoimmune uveitis (inflammation of the eye)

**E.C.G.:** electrocardiograph a recording of heart waves.

**E.E.G.** Electro Encephalographic Recording is a test to record electrical brain waves to help diagnose Epilepsy, sleep disorders and brain death.

**E.S.R.** test used to measure inflammation, infection (10 – 15 mm is normal)

**Fibromyalgia:** (FMS): A autoimmune disease affecting the fascia.

**F.D.A** Food and Drug Administration (agency monitoring safety of new drugs through drug trials)

**F-wave** is a variable response and is obtained infrequently after nerve stimulation. Commonly, several supramaximal stimuli are needed before an F-response is seen since only few stimuli reach the anterior horn cell at the appropriate time to stimulate it.

**G.B.S.** Guillain-Barre Syndrome, sudden or slow onset of weakness after flu due to autoimmune disease.

**Gingivitis:** Inflammation of the fibrous tissues that surround the teeth.

**Glucose:** A sugar that is the simplest form of carbohydrate. It is commonly referred to as blood sugar. The body breaks down carbohydrates in foods into glucose, which serves as the primary fuel for the muscles and the brain.

**HAART:** A therapy, composed of multiple anti-HIV drugs, which is prescribed to many HIV-positive people, even before they develop symptoms of AIDS .

**HIV:** Abbreviation for human immunodeficiency virus, a retrovirus associated with onset of advanced immunodeficiency syndrome (AIDS).

**Hormones:** Chemical substances secreted by a variety of body organs that are carried by the bloodstream and usually influence cells some distance from the source of production. Examples include adrenal hormones such as corticosteroids and aldosterone; glucagon, growth hormone, insulin, testosterone, estrogens, progestins, progesterone, DHEA, melatonin, and thyroid hormones such as thyroxine and calcitonin.

**Horners:** Horner syndrome is a small pupil (miosis), droopy eyelid (ptosis), and shrunken eyeball (enophthalmos) and reduction of sweating on the ipsilateral side of the face and neck,; occasionally the development of cataracts; same side loss of sweating (hemifacial anhidrosis) .

**H.S.P.** Heat shock proteins (HSPs), also called *stress proteins*, are a group of proteins that are present in all cells in all life forms. They are induced when a cell undergoes various types of environmental stresses like heat, cold and oxygen deprivation.

**Hyperkplexia:** Startle disease (hyperekplexia) is a rare non-epileptic disorder characterized by hypertonia, generalized stiffness and brief muscle jerks in response to unexpected auditory, somatosensory and visual stimuli.

**I.C.** Interstitial cystitis a bladder infection induced autoimmune disorder

**Immune System:** A complex that protects the body from disease organisms and other foreign bodies.

**I.O.I.** Intraocular inflammation of the eye

**Irritable Bowel Syndrome:** (IBS) A condition that causes upset intestines with pain in the lower abdomen; bloating , alternating diarrhea and constipation; mucous in stools; indigestion; constant tiredness; low back pain; painful intercourse in women.

**I.V.I.G.** Intra Venous Immune Globulin a solution containing IgG antibodies from Humans.

**Leukemia:** Cancer of the lymph glands and bone marrow resulting in overproduction of white blood cells (related to Hodgkin's disease).



**Leukocyte:** A white blood cell which appears 5,000 to 10,000 times in each cubic millimeter of normal human blood. Among the functions are destroying bacteria, fungi and viruses and rendering harmless poisonous substances that may result from allergic reactions and cell injury.

**Lyme disease** caused by a spirochete called **Borrelia burgdorferi**. First recognized in the United States, following a mysterious outbreak of juvenile rheumatoid arthritis near the community of Lyme, Connecticut.

**Metabolism:** The chemical processes of living cells in which energy is produced in order to replace and repair tissues and maintain a healthy body. Responsible for the production of energy, biosynthesis of important substances, and degradation of various compounds.

**Mold:** Molds are Fungi which produce allergens (substances that can cause allergic reactions), irritants, and in some cases, potentially toxic substances (mycotoxins). Inhaling or touching mold or mold spores may cause allergic reactions in sensitive individuals. Allergic responses include hay fever-type symptoms, such as sneezing, runny nose, red eyes, and skin rash (dermatitis). Autoimmune reactions to mold are common.

**M.R.I.** Magnetic resonance imaging scan used to make pictures of the body by using magnets with a computer.

**MTHFR** stands for **Methylene-Tetra-Hydro-Folate-Reductase**. MTHFR is an enzyme it is needed to metabolize and get rid of homocysteine. High homocysteine levels are a risk factor for blood clots in the veins or arteries. Levels of homocysteine can be lowered by taking a multiple vitamin with a high content of folic acid (400 mcg = 0.4 mg), vitamin B6 (pyridoxine; 25 mg) and B12 (cobalamin; 1 mg).

**N.I.H.** National Institutes of Health (Medical Research Agency in USA)

**O.C.D.** Obsessive-compulsive disorder an autoimmune psychiatric disorder

**Parasite:** An organism living in or on another organism.

**PFOA** stands for Perfluorooctanoic Acid, a man-made chemical. PFOA (sometimes also called "C8") is used by companies, such as DuPont (Teflon, Stainmaster, Scotchguard), to make fluoro-polymers for use in non-stick cookware and all-weather clothing. PFOA have been commonly found in humans across the globe

**PLEDS:** Periodic lateralized epileptiform discharges (PLEDs) are seen, as a rule, following acute brain damage. (These are large EEG waves present over one are of the brain

**Pyelonephritis:** Inflammation of the renal pelvis.

**Raynaud's phenomenon** Raynaud's phenomenon, called Raynaud's syndrome, is a disorder of blood circulation in the fingers. Exposure to cold reduces blood circulation causing the fingers to become pale, waxy-white or purple. Raynaud's most commonly associated with hand-arm vibration syndrome but it is also involved in other occupational diseases.

**Rickettsia:** Bacteria, are carried as parasites by many ticks, fleas, and lice, and cause diseases such as typhus, rickettsialpox, Brill-Zinsser disease, Boutonneuse fever, Rocky Mountain spotted fever, and endemic typhus in human beings. Like viruses, they grow only in living cells.

**Rituximab:** The first monoclonal antibody therapy approved in the United States for the treatment of relapsed or refractory non-Hodgkin's lymphoma (NHL).

**E.S.R.** Erythrocyte Sedimentation Rate or **E.S.R.** test used to measure inflammation, infection (10 – 15 mm is normal)

**Syndrome** number of symptoms described together, Example; dry eyes and dry mouth is Sjogrens syndrome.

**Tilt Test:** Individuals with syncope are placed on a Tilt table and their blood pressure and pulse is monitored. If the individual gets symptoms or the blood pressure falls after standing up then the test is

considered positive.

**TMJ:** Temporo-mandibular joint - hinge of the. This gets tight jaw usually due to muscle pain

**Urea breath test** Is a procedure for diagnosing the presence of a bacterium, *Helicobacter pylori* (H. pylori) that causes inflammation, ulcers, and atrophy of the stomach.

**Virus:** Any of a vast group of minute structures composed of a protein coat and a core of DNA and/or RNA that reproduces in the cells of the infected host. Capable of infecting all animals and plants, causing devastating disease in immunocompromised individuals. Viruses are not affected by antibiotics, and are completely dependent upon the cells of the infected host for the ability to reproduce.

**White Blood Cell:** (WBC): A blood cell also called as leukocyte that does not contain hemoglobin and is responsible for maintaining the body's immune surveillance system against invasion by foreign media.

## - Chapter 1 Introduction to Inflammation (the flame within)

The number one disease process in the world today is autoimmune diseases (AD). The autoimmune diseases have surpassed heart disease, cancer and diabetes which used to be the leading causes of disease in the past. Today nearly all heart disease, diabetes and some of the cancers are triggered by inflammation. This inflammatory relationship is revolutionizing the treatment of cancer and AD. If diagnosed early with an autoimmune process, people can get better faster and expect to live longer and healthier life.

Autoimmune diseases tend to affect women three times more than men. Women have a robust immune system as compared to men; and it acts as a double edged sword. Females get less infections but more autoimmune diseases. Males get more infections have less autoimmune disease but by the age of forty they start to get pains and numbness in the feet caused by autoimmune neuropathy. This numbness usually gets misdiagnosed as a diabetic polyneuropathy, in a few years this untreated inflammation will take the life of this misdiagnosed individual. Men start falling prey to autoimmune diseases in mid life as their testosterone levels falls, they also get exposed to chemicals and bugs. Stress becomes a big factor and their diet becomes poor with increased use of alcohol.

Autoimmune skin lesions get misdiagnosed as herpes and individuals are placed on acyclovir without any help. The most common symptom of autoimmune disease is fatigue. Women with fatigue never get an evaluation for autoimmune disease and suffer unnecessarily.

Chronic inflammation, spurred by the immune system, plays a role in majority of medical diseases (evils) including arthritis, Alzheimer's, multiple sclerosis, diabetes, cancer and heart disease.

Microorganisma like *Chlamydia pneumonia* (*Mycoplasma*), *Helicobacter-pylori*, *Borrelia Burgdorferi*, and mold (Fungus) are important triggering events for autoimmune disease (AD). The AD can also be triggered by stress, excessive physical activity, surgery, food (gluten), vaccination and trauma due to accidents. These events will only be triggered in genetically predisposed individuals, who have a tendency to develop autoantibodies (antibodies that attack self proteins). *Helicobacter pylori* (H.pylori) is a bacteria which has developed with the humans, it is present in the stomach linings of humans worldwide,

known for causing stomach ulcers, skin diseases and developing stomach cancers. Green tea, milk and yogurt have been found to inhibit its growth. We have discussed how to eliminate h-pylori and similar pathogens in the gastrointestinal chapter.

The flame within us is waits to be turned on by a rogue protein, that we eat, a infection or by exposure to chemicals. Some diseases get turned on in specific decades of life.

Kawasaki and childhood epilepsies get turned on, in the first decade of life, others like multiple sclerosis and S.L.E. are activated in the second decade, while Alzheimers and ALS are turned on in the last decades of life.

There is an association of Kawasaki disease to carpet shampoo exposure, even a spot cleaner no matter what brand will trigger off this deadly disease. Kawasaki is also triggered by the placement of a humidifier in the child room. We recommend cleaning the carpets with hot water only specially with a infant is in the house.

Prevention is key, simply by consuming an anti-inflammatory diet, enjoying mild physical activity and by losing the fat, which pumps chemicals which drives inflammation. Early onset alopecia, arthritis and CNS vasculitis are seen more commonly in repeated consanguineous marriage (cousin marriage). There have to be multiple factors involved in falling prey to autoimmune diseases. A product of multiple cousin marriage, and then gets a trivial head injuries is enough to fire off the immune system.

Inflammation is not always considered harmful. Inflammation is part of the typical immune response which is essential for battling germs and healing wounds. The familiar redness, heat, swelling and pain from, any injury or a splinter are signs of inflammation helping protect us. Problem starts, when the inflammatory process fails to shut off, after an infection or injury is over. Persistent, low level inflammation paves the way, for the chronic autoimmune diseases in later life. Persistent inflammation is probably, the reason why men and women at around age forty start experiencing more autoimmune diseases. To prevent low level inflammation, a daily aspirin, fish oil or a balanced diet can be used.

Chronic inflammation is similar in all AD such as, cardiac, kidneys, arthritis, lungs (asthma) or brain (epilepsy, alzheimers). They are all caused by an antibody mediated diseases process, “inflammatory” and the treatment is similar for all these diseases, “anti-inflammatory” or immune modulation. Modulation here means to modify the immune system by medication supplements or lifestyle change.

Heart attacks, in the past have been related to the cholesterol problem. Blood vessels became clogged with atherosclerotic plaque called "bad" (LDL) cholesterol, which was deposited on vessel walls. Current thinking has changed, scientist have discovered, the misguided immune system targets a blood vessel, resulting in inflammation within arteries, where cholesterol then gets deposited, narrowing the vessel. The site of inflammation, in a blood vessel, is the place where cholesterol gets deposited and eventually blocks it. Center of Disease Control reports, Mycoplasma pneumoniae (MP) and Chlamydia pneumoniae (CP) within the blood vessels of the heart, results in inflammation and blockage. Inflammation is now seen as the cause of heart disease. To test the level of inflammation within the body a test called **CRP** (C-reactive protein) is done. American Heart Association

has raised awareness that bacteria like **Chlamydia pneumoniae**, **Helicobacter pylori** are the cause of inflammation in heart disease. The complete discussion on how to get rid of these bacteria in heart disease is provided in the cardiac chapter.

Diabetes is linked to inflammation; the immune system attacks the pancreatic islet cells that make insulin and reduces the production of insulin. This is discussed further in the endocrine chapter.

Two studies which show that sewer rats had better immune systems than rats living in antiseptic labs, the lesson for humans are that clean living may make us sick. These studies gives weight to a 17-year-old theory that the sanitized Western world may be partly to blame for soaring rates of human allergy and asthma cases and autoimmune diseases, such as Type I diabetes and rheumatoid arthritis. The Hygiene Hypothesis," is that children who are around numerous other children or animals early in life are exposed to more microbes, and their immune systems develop more tolerance for the irritants that cause asthma. Those who do not get these exposures in childhood start to react abnormally to irritants in later life.

Diet is an important factor in reducing inflammation, as processed foods and trans-fats increases inflammation. A diet rich in fruits and vegetables helps in reducing the inflammation, the fibers increase intestinal motility, which helps reduce inflammation as toxins like H-pylori are quickly moved forward and less of them get absorbed into the body. A low fat diet combined by heavy exercise is detrimental for the immune system. Dietary fats are not the cause of disease, but inflammation is. Include these good fats in your diet, such as salmon, walnuts, milk fat, butter oil, corn oil, olive oil, coconut oil, canola oil and fish oil.

It is recommended that people over forty take a baby aspirin daily (to suppress the smoldering inflammation, avoid aspirin if you have a bleeding disorder or gastric ulcers. Fish oil or high content of omega-3 taken daily also suppresses inflammation. People taking these supplements show lower values on the CRP test. We believe that once a low dose anti-inflammatory combined with the recommended diet used daily, may help prevent inflammatory diseases later in life.

The size of an individuals belly is an important risk factor for disease. An unhealthy weight will trigger an inflammatory reaction. Excess weight causes hypertension, insulin resistance resulting in a high cholesterol levels. By lowering weight one can lower the risk of heart disease as hypertension, cholesterol and insulin resistance, all go away.

**The Attack on Self Tissues:** Immune cells are the protective force maintained in our body. The immune system which gets tricked into attacking self tissues, usually by bacteria, triggers an autoimmune disease. Every cell in the body has a specific protein tag (antigen), bacteria entering our body carry antigens similar to cells in the human body. The immune system develops specific antibodies to target these bacteria, the antibodies attach to the bacteria and eliminate them. However, some antibodies also attach to body cells that carry similar antigens the bacteria. The cells where a antibody has attached are destroyed by the immune system. In early stages of the disease the body tries to repair the damaged tissue. If the repair is effective, the person feels better, which is called a remission. If the body is exposed to the bacteria again, then a second attack takes place and the person feels weak again, this worsening is called a relapse.

Autoimmune diseases can affect the body in different ways. For instance, an autoimmune attack is directed against the brain in multiple sclerosis and the gut in crohn's disease. In other diseases, such as systemic lupus erythematosus (SLE), any part of the body can be attacked. (Heart, lung, kidney, brain, intestines, skin, muscles). Some of the autoimmune diseases are considered rare. However as a group these diseases afflict millions of people.

### **Stages of autoimmune disease: (Khans inflammatory staging)**

**Inflammatory stage:** All the autoimmune diseases usually have three stages the first stage when the attack is just starting and the disease has flare-ups. This is described as remitting-relapsing type disease. The individual has good and bad days. We have termed this the **inflammatory stage** of an autoimmune disease. In this phase the body cells are under an inflammatory attack. Biopsy of tissue obtained in this stage will show some inflammation, some repair (fibrosis) and some atrophy. A combination of atrophy, repair and inflammation in is the hallmark of all autoimmune diseases. Similar tissue reactions are observed in polymyositis, atrophic gastritis, and inflammation of the ovary (oophoritis). In the inflammatory stage active treatment can stop the disease process if the offending pathogen can be removed while suppressing the immune attack by medications. Usually this stage lasts up to the first 15 months following the first symptoms. If the individual is fully functional with a active autoimmune disease, then they are in the inflammatory stage of disease.

**Stable stage:** In the stable phase a autoimmune disease is active but no new attacks are taking place. Disease activity can be measured by the CRP which will be elevated in active disease. In the case of MS it can be monitored by symptoms or MRI scans. In the stable stage the individual needs to be continued on immunomodulatory treatment, as long as the CRP or erythrocyte sedimentation (ESR) rate stays above normal.

**Progressive Stage:** After being in the inflammatory stage without treatment, the autoimmune diseases can enter a progressive stage. This will not be seen in all the individuals as many may receive antibiotics for an infection, anti-inflammatory treatments and others improve spontaneously. Spontaneous improvement is termed disease burnout, some how the immune attack resolves. In this stage remissions and relapses are not present, and there is just a progressive down hill course. Some diseases like Multiple Sclerosis take a few years to enter this phase others like Giant cell Myocarditis enter this phase within a few weeks of onset. In the progressive stage of disease treatment should be high dose and aggressive.

### **-Chapter 2 Causative factors in autoimmune disease:**

Autoimmune disease incidence is much higher in the western world and may be linked to the western diet (high in processed foods and calories) or high chemical exposure. Children who did not get colostrum (premi milk produced after pregnancy), are at risk of getting more infections and higher risk of autoimmune diseases. Children who spent their third semester in uterus during the winters while their mothers were exposed to infections also show a slightly higher rate of autoimmune disease. Children should get mothers milk for at least

two years. Colostrum has strong anti-inflammatory properties and is produced from the mammary glands after the termination of pregnancy. Fresh colostrum is packed with antibodies, growth factors, and nutrients. The mother is passing a lot of her antibodies to the baby. This is a natural vaccination against diseases.

**Genetic Factors:** The genes people inherit contribute to their susceptibility for developing an autoimmune disease. Individual family members with autoimmune diseases may inherit and share a set of abnormal genes, although they may develop different autoimmune diseases. Mother may have diabetes, the daughter gets vasculitis and granddaughter may have iritis.

The autoimmune diseases are often chronic, requiring lifelong care and monitoring. Currently few autoimmune diseases can be cured or made to "disappear" with treatment. Myasthenia Gravis can be cured in some individuals with the removal of Thymus Gland in the neck. Kawasaki disease in children can be cured if IVIg is provided soon after the diagnosis. Early treatment in autoimmune diseases has resulted in long term remissions. Many people with autoimmune diseases live normal lives.

**Diet:** Inflammation can be triggered by an inadequate diet, which is deficient in nutrients but has excess in toxins. In many conditions like Alzheimer's, Epilepsy, Migraine, Fibromyalgia, ALS and chronic fatigue there is a magnesium deficiency seen in individuals. Deficiency of magnesium is associated with a higher CRP level, which if left untreated will trigger autoimmune diseases. Magnesium supplements are used to stop epilepsy attacks. Magnesium is deficient in individuals who eat white flour, only 16% of magnesium is left in white flour when compared to whole wheat. Depressed individuals given magnesium supplements show a sudden reversal of symptoms.

Aluminum exposure has resulted in osteoporosis due to magnesium and calcium deficiency. Buffered aspirin contains aluminum, antacids and anti diarrhea products contain aluminum. People with chronic renal failure treated with aluminum-containing medications and pre-term infants fed on aluminum containing formula are at high risk of aluminum toxicity. The healthy human body can defend itself adequately from aluminum's toxic effects, but long term exposure should be avoided. Vitamin deficiency like, Cyanocobalamin (B12), Folic acid, Pyridoxine (B6), Thiamine (B1) and Vitamin-D have all been associated with inflammation. In the entire western world there is a higher incidence of Multiple Sclerosis. The countries with a higher incidence of MS have the lowest amount of sunlight year round. Reduced sunlight in turn causes vitamin-D deficiency, supplements of vitamin-D independently improve symptoms of MS.

Homocysteine is an intermediate compound formed during metabolism of methionine (an amino acid). Elevated serum homocysteine levels are a known risk factor for coronary artery disease, chronic inflammatory disease and multiple sclerosis. The plasma levels of homocysteine are dependent on the intake of folic acid, vitamin B6 (pyridoxine), and vitamin B12 (cobalamin). We have no accurate laboratory test to measure minimum levels of B12 deficiency. Even if lab tests show a normal range of B12 and serum folate levels,

the body may actually be deficient. A more sensitive indicator is **homocysteine**, if homocysteine levels are high then sub-lingual supplements of vitamin B12, B-6 and folic acid help reduce serum homocysteine concentrations, while also reducing the risk of myocardial infarction and stroke.

**Sunshine & Environment:** Many of the autoimmune disorders are triggered by excessive cold, protective clothing is required in cold weather. Summer heat and the hot Sun in the afternoon will trigger some of the skin disorders, proper protection from the hot afternoon sun is a requirement. Skin turning red under the sun is a sign of inflammation which should be avoided. Nerve disorders like facial palsy are triggered by cold exposure. Multiple sclerosis and neuropathy are aggravated by heat exposure. Extremes of temperatures will produce *stress proteins* which causes inflammation in the body. To read more about stress proteins please see the immunology chapter. Sunlight stimulates the pineal gland in the brain, pineal produces certain chemicals called 'tryptamines'. The human body requires a prolonged exposure to the sun to produce vitamin-D and keep our mood happy with the tryptamines. Avoid routine use of sunglasses, especially on cloudy days, to obtain more sunshine for the Pineal gland.

**Vaccination:** The association of vaccination and resulting autoimmune disease is well known. The Centers of Disease Control (C.D.C.) reported an association between flu vaccine and Guillian Barre Syndrome (GBS). The affected person in whom the disease is triggered by a vaccine should get steroids or IVIg quickly, the whole triggered disease process will resolve. Physicians need to be aware that potential treatment exists. The incidence of GBS after flu vaccine is usually seen within the first 6 weeks. Fortunately incidence is low at 9 cases of GBS per million vaccines given. Post vaccination GBS is also reported with tetanus toxoid and tetanus-diphtheria toxoid. The reaction happens most likely due to antibodies present in the vaccine triggering an autoimmune response against self. If someone develops a reaction don't wait ask for IVIg or 100-mg of prednisone. Thimerosal is a mercury-containing preservative which was linked to autism. Today, with the exception of some Influenza (flu) vaccines, none of the vaccines used in the U.S. to protect preschool children against 12 infectious diseases contain thimerosal as a preservative.

**Injury:** Injury has been studied for many years as a cause of autoimmune disease. Railway spine was a term used in early 1900 for chronic pains seen in people following a railway accident that was later termed the railway brain as a way for people seeking compensation. The railway spine condition was discredited. However the modern malady of Fibromyalgia is similar to the railroad spine and is triggered by an injury and considered a valid entity. For over a century, individuals and physicians have dealt with the phenomena that trauma may precede the onset of multiple sclerosis but multiple studies have failed to show such a relationship. The literature does show Pemphigus, Fibromyalgia, eye injury (sympathetic ophthalmia), renal failure (glomerulonephritis) and long term neuropathies are triggered by trauma. Multiple studies from earthquake injured personnel show long term sensory motor neuropathies caused by trauma. Scientists think swelling in the anterior and posterior compartments at the time of injury, in the leg caused the neuropathies. These observations are helpful for future prevention of autoimmune disease, by administering a dose of

prednisone at the time of injury may prevent these nerve injuries. Today there is another explanation to address this issue, which is by activation of stress proteins at the time of injury.

An injury triggers an immune reaction, just look at the swollen feet of an injured athlete. No bones are broken, the muscles are intact and the swelling is a immune reaction. In an injury the naturally protected proteins in the body get exposed to the immune system. Following the exposure the immune system mounts an attack against them. After any head injury inflammation develops in the brain, this may be triggered by *stress proteins*. The head injury may not be seen on a MRI scan but the rise in inflammation can be measured by the C-reactive protein test. Steroid treatment following a injury prevents *stress proteins* from activating. Steroids used at the time of injury result in a lower incidence of autoimmune disease later in life. Please read the immune section for HSP proteins.

**Stress:** Stress can trigger autoimmune disease and which is quite common, *stress proteins* are produced by the cells, which triggers inflammation within the body. Stress related neuropsychiatric disorders like P.T.S.D. (post traumatic stress syndrome) are associated with immune system activation, resulting in inflammation. Healthy people living in conditions of chronic stress frequently show lower urinary and plasma cortisol. This can happen following a sexual assault, car accident, chronic job stress (soldier, policeman, and fireman) or being in a natural disaster. Once the cortisol levels are depressed, inflammation markers like CRP start to going up. In one study done on women exposed to stress their CRP levels were found to be elevated. People with chronic fatigue syndrome and Fibromyalgia have lower levels of cortisol. In untreated PTSD individuals with lower cortisol levels and high rates of inflammation, paves the way for autoimmune diseases. Stress lead to early symptoms of stiffness, neck pain and difficulty sleeping. Early intervention by restoring the normal levels of cortisol can stop the stress process. The correct medicine to stop stress will be a prednisone or (DHEA - Dehydroepiandrosterone,) rather than routine psychiatric medications which not relive the inflammation associated with PTSD, thus we see the high mortality as a result of suicide, often in servicemen returning from war duty.

**Excessive Exercise and Low fat a bad combination:** Excessive exercise has resulted in athletes to develop autoimmune diseases. Chronic fatigue, CIDP, ALS are among the diseases which develop after excessive exercise or activity. Moderate exercise enhances the immune status, but when athletes exercise to the maximum, it stresses the immune system, especially when they are training heavily and don't get enough rest, this leaves them susceptible to neuro-muscular diseases. Switching from a low to moderate fat diet dramatically increased the number of natural killer cells, according to a research study. The study shows, “**that a low-fat diet**, adhered to by many competitive athletes, may not be best for the immune system, by increasing dietary fat to moderate levels improves the immune functions. Lowering fat in the diet triggers higher cholesterol levels which results in more inflammation. To lower body cholesterol we need to increase good dietary fat, this is a inverse relationship poorly understood by physicians and the lay people alike.



The most commonly reported autoimmune disease in athletes is cardiomyopathy (CM) which initially present with dizziness. CM is a dangerous condition which requires immediate rest for 2-3 months duration. Inflammation usually triggered by a low-fat diet and over exercise results in CM. For the management of athlete-myocarditis please read the cardiac section. Before any exercise the body needs to be well hydrated, the body needs normal **fat**, protein and carbohydrates for the intense metabolism. Majority of the people who start an exercise plan, combined with a low fat low carbohydrate diet will lead to the release of excessive *stress proteins*, and this will cause more stiffness and weakness in the muscles. Our bodies require more omega-3 type fats and less omega-6. The correct proportion was placed by nature in whole wheat bread.

**Chemical Exposure:** Single or repeated chemical exposure can result in autoimmune diseases. Exposure to fumes, toxins and pesticides is well known. In infants even a single exposure to carpet shampoo will trigger Kawasaki disease. Fluoridated water or chlorine can cause Myasthenia Gravis. Pesticides have been linked to cause Parkinsonism. Chemicals are everywhere and also contained in drugs. In a recent study, done on people who had been exposed to amphetamines (drugs used for sleep disorders and attention disorders) they found a relationship between the amphetamine and development of Parkinsons. Tobacco smoke contains a mixture of over 4700 chemical components many of which are toxic and have been implicated in the etiology of chronic obstructive pulmonary disease, asthma, cancer and cardiovascular disease. Some chemicals like Agent Orange not only give rise to autoimmune diseases, but parents exposure to Agent Orange appears to be associated with an increased risk of birth defects in their children. A drug called MPTP caused Parkinson in a famous movie star and many young people, which is an autoimmune triggered reaction of the drug to the substantia-niagra (dopamine producing region in the brain) which can improve with immunomodulation. A higher incidence of Parkinsons is seen in gardeners and farmers directly linked to pesticides. Chemicals activate *stress proteins* which results in inflammatory diseases. Single or multiple exposures to chemicals can cause an autoimmune reaction to be triggered in genetically predisposed individuals. Pesticides induced problem can be avoided by using gloves, masks and taking a shower soon after work.

Multiple sclerosis (MS) has a higher incidence in individuals with dental amalgam which contains **mercury** and silver fillings. Significant deposits of **mercury**, previously non-existent, have been found in the lungs, kidneys, endocrine organs, liver, and heart of individuals with amalgam. Amalgam has not only been associated with heart disease but also M.S. and cancer. Mercury and silver absorbed from the amalgam can easily be removed by taking cilantro.

A chemical analysis of the cord blood done in infants showed 270 different chemicals were found in an average baby's blood. These chemicals can harm the development of the brain and nervous system, cause skin rash, allergies, cancer, birth defects, liver and kidney damage. The toxins include mercury, flame retardants and pesticides. In an average kitchen storage we see carpet cleaners, window cleaners, and grill cleaners these are all toxic. If you can smell them you are inhaling them. Infants are particularly vulnerable as their immune system is developing and these chemicals can cause immune dysfunction. PFQA a

chemical in Teflon finds its way to the baby in the uterus. PFOA takes years to leave the body and can be found in the environment and animals as far away from sources as polar bears in the Arctic and dolphins in the Mediterranean. Traces of PFOA have been found in individuals all over the world. EPA began its investigation into PFOA, they found it is very persistent in the environment, PFQA was present at very low levels both in the environment and in the blood of the general U.S population. Though only trace amounts of PFOA exist in Teflon products when they hit the market, some scientists believe the chemical may be released as Teflon ages. Other scientists have suggested that PFOA, which is also used in stain and grease-resistant carpets, clothing and fast-food packaging, may be released into water supplies when carpets or clothing are washed. Children can crawl and lick the carpets. PFOA is found in french-fry boxes, microwave popcorn bags, and hamburger. Bisphenol is used in polycarbonate plastic baby bottles and in resins that line food cans, it has been found to alter brain structure, neurochemistry, behavior, reproduction and immune response in animals.

**Poisoning:** The most common cause of poisoning in the US is exposure to carbon monoxide. Carbon monoxide exposure not only results in a reduction in Oxygen saturation but it also triggers an inflammatory response. The inflammatory response is seen from after any chemical exposure including diesel and kerosene fumes. Food poisoning may also trigger autoimmune diseases. If the symptoms following any poisoning do not improve with treatment, then a CRP test should be done to look for inflammation, if CRP is elevated then inflammation should be treated with aspirin, steroids or IVIg. Heavy metal intoxication with gold, mercury, and manganese, are known stimulants of the immune system and have been implicated as a cause of autoimmune diseases.

**Single Biggest Cause the infections & Molecular mimicry:** There are lots of bacteria and viruses around us which will trigger autoimmune diseases (**Helicobacter pylori, Chlamydia pneumoniae**). We do not have to worry about getting them we already have them in our body. People who put metallic objects in their mouths have higher counts of these organisms. Once an organism enters our body the immune system recognizes the biological identification markers on this invader. An attack is mounted but sometimes this attack damages our own body.

Molecular mimicry is one mechanism by which infectious agents can trigger an immune response against self. According to this hypothesis a host acquires an infection with an agent that has antigens that are similar to the host antigens but differ sufficiently to induce an immune response. The resulting immune response will attack the infecting organism and damage specific host cells that resemble the antigen. A scientist found that a infection with a rotavirus, a type of gastro-enteritis which infects almost all young children, may trigger type I (childhood) diabetes in susceptible individuals. It was noticed that some parts of the virus proteins are very similar to proteins on the surface of pancreatic cells. Because of this similarity, the body's immune system could attack both the invading virus, and the body's own pancreatic tissues. Diabetes-I develops, when the immune system attacks pancreatic cells, reducing the production of insulin. It was found that the children who went on to develop diabetes experienced a big jump in anti-pancreatic antibodies every time they

became infected with rotavirus. Molecular mimicry of the pancreatic proteins by the Rotavirus may cause the immune system to attack the pancreatic cells.

Idiopathic thrombocytopenic purpura (ITP) a blood disorder that causes destruction of the small sticky platelets, is caused by autoantibodies sticking to platelets which leads to platelet destruction, has been associated with *Helicobacter pylori*. Myocarditis (heart enlargement) is triggered off by Coxsackie-virus, Cytomegalo-virus and streptococcus. Ankylosing spondylitis (arthritis) is triggered by *Yersinia* or *Salmonella*. Multiple Sclerosis can be triggered by Epstein-Barr-Virus, Coronavirus, *Acinetobacter* and *Pseudomonas aeruginosa*.

Early infection should be promptly treated and a full course of the antibiotic should be taken, to effectively eradicate any low grade infection. Antibiotic treatment helps prevent the triggering of autoimmune disease. You will read about the recommended antibiotics in the disease sections.

In a large study a group of American dental patients were studied by measuring their CRP. The CRP which measures inflammation was elevated with extensive periodontal disease. Regular cleaning of the teeth and gums helps to stay healthy. Dental disease is associated with higher risk of heart disease, stroke and infections.

The best prevention is to wash your hands before you eat or touch food. Kissing can easily spread thousands of bugs present in the mouth. (Intimate kissing with multiple partners) has caused some serious infections like meningococcal disease. Infectious mononucleosis (mono) or glandular fever is often called the kissing disease, but more commonly coughing, sneezing, or sharing a glass or cup transmits mononucleosis. Similarly infections have originated after the people have kissed their pets. Pets should not be allowed near new born who have a weak immune system. Sex with multiple unprotected partners should be avoided. Multiple partners expose you to multiple types of the organisms, especially those who have metallic objects in their genitals.

**Pharmaceutical triggers:** Some of the medications like minocin, IVIg, anti-cholesterol medications including statins can induce inflammatory diseases which are reversible after discontinuation of the drug.

**Immune reconstitution inflammatory syndrome (IRIS):** This is a condition seen in some cases of AIDS or immunosuppression, in which the immune system during recovery from the infection, responds to a previously acquired infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse. A sudden increase in the inflammatory response produces nonspecific symptoms such as fever, and in some cases a worsening of damage to the infected tissue. Though these symptoms can be dangerous, they also indicate that the body may now have a better chance to defeat the infection. The most common treatment is to administer antibiotics or antiviral drugs against the infectious organism, and in some cases corticosteroids to suppress inflammation until the infection has been eliminated.

Infections most commonly associated with IRIS include cytomegalovirus, herpes-zoster, Mycobacterium avium complex (MAC), Pneumocystis-pneumonia, and tuberculosis. AIDS individuals are more at risk for IRIS when they are starting HAART for the first time, or if they have recently been treated for an opportunistic infection.

### **- Chapter 3     Diagnosis of Autoimmune Disease**

Autoimmune diseases can be diagnosed easily based upon history. The symptoms described by the individual are an important clue. Once the physician gets the clue from the history then just a specific examination of the particular individual will get the diagnosis. We have described the specific examination findings under each disease. Rarely some special lab tests are required which are described under each disease.

**Some early symptoms of autoimmune disease:** Autoimmune diseases commonly affect women in nearly all age groups. Combined together autoimmune diseases are the number one killer of women in the world. This is the biggest terror threat to women. The symptoms start with complaints of **fatigue** and tiredness, followed by feeling of pain numbness and weakness. Individuals have difficulty in concentration. Visit to the doctor's office will result in normal evaluations. Generally the doctor will refer the individual to a psychiatrist or start antidepressants. In the short run any prescription or placebo may seem to help. The autoimmune diseases are remitting and relapsing so no matter what drug is used the individual will enter a "remission phase" refers to the situation where the disease disappears completely.

Diagnostic clues seen in autoimmune disease are symptoms which, "**remit and relapse**" or "wax & wane". The individual may have weakness, fatigue for a month and then they feel better for the next month. Remitting and relapsing disease is commonly seen in Multiple Sclerosis, Fibromyalgia, Chronic Fatigue and Obsessive Compulsive Disorder. Any treatment given at the start of a remission may seem to help, one has to observe the treatment for a year or more to see if the disease relapses (comes back).

Autoimmune diseases behave like the stock market, some symptoms become worse on some days while other ones improve. The up and down cycles in a disease process should alert the physician of an underlying autoimmune disease process. **These cycles are a diagnostic marker for autoimmune disorders.** There are days similar to a stock market collapse when all the symptoms are worse.

When a person has multiple complaints consisting of fatigue, tiredness, reduced energy, pain and stiffness then a diagnosis of autoimmune diseases in general, and Fibromyalgia, Chronic Fatigue and S.L.E in particular should be considered.

**Some autoimmune symptoms, with possible causes and strategies to avoid them:**

**Insomnia, Fatigue & memory problems:** The person feels tired all the time and does not sleep well. The little energy the person has gets worse with activity. In the morning it feels like a truck ran over the body. The feeling is there as the affected person does not obtain a good night sleep. People with fibromyalgia and arthritis have poor sleep in stages 2 & 3 of sleep, supplements of magnesium and DHEA help improve these symptoms. For details please look in the fibromyalgia section.

**Depression:** Depressed individuals have difficulty in doing their day to day tasks. During the day they appear overwhelmed and demonstrate stress which turns into depression. Depression is caused by inflammation and low serotonin levels in the brain. Tryptophan in the milk can be activated by warming the milk, on drinking warm milk, in the body it is converted to serotonin. Consumption of warm milk helps overcome the symptoms of depression. Tryptophans are also present in brown rice, yogurt, cheese, meat, peanut and sesame seeds or try getting a tryptophan supplement. To reduce inflammation seen in depression, take a good diet combined with supplements of fish-oil, aspirin or steroids may help. Please see the chapter on depression and PTSD for more help.

**Gastrointestinal Problems:** Some people will have symptoms of gas, bloating, cramps, diarrhea, constipation and irritable bowel syndrome. This is because their stomach cannot tolerate digesting a large meal or they are allergic to some food. The meals stay longer in their stomach, causing fermentation and gas buildup. These individuals may need to eat small snacks in place of large meals and avoid any allergens to eliminate their symptoms. Remember to eat proteins and carbohydrates at different times, taken together they will cause fermentation and gas in some individuals. If this does not help then try eating a diet of fruits, vegetables, milk products, chicken, beef and fish for four months. (No gluten, no wheat, rye, barley, millet or oat. (No beer). Use honey in the morning and **yogurt** three times a day to help with gastric motility problems. Read the diet section for more help.

**Chemical Sensitivity & Allergies:** When the immune system becomes dysfunctional then the body starts to react abnormally to various toxins, which is a common reaction seen in the western countries. Chemical exposure to new carpet smell will cause headaches and fatigue, tiredness and pain. To reduce chemical sensitivities, use cilantro to eliminate toxins, DHEA to reduce the inflammatory response and check the diet page which guides you to avoid toxins and eat the proper whole foods.

**Pain:** The most common cause of pain in the whole world is myofascial pain disorder. In myofascial pain parts of the muscle fibers form knots called trigger points which result in pain. These trigger points are seen with every autoimmune disorder, common in MS, Parkinsons and arthritis. Try to stretch your joints first thing in the morning and every three hours during the day. Magnesium supplement may help reduce stiffness and please read the diet section and muscle stiffness section for detailed help.

**Dry Eyes:** Most of the autoimmune disorders cause reduced tear production, eyes get dry and become light sensitive. Keeping the eyes moist and using sunglasses during the day with consumption of fish oils, aspirin or steroids help reduce inflammation and dryness. Please read the Sjogrens chapter for more information.

**Loud Sounds:** cause a startle. Ears become hypersensitive and they can not pay attention to one speaker in a crowd. This is due to the Stapedius muscle going into a spasm. Most frequently seen in Stiff person syndrome, fibromyalgia and myofascial pain disorder involving the neck, usually the excessive startle will respond to vitamin B-12 and magnesium supplements and by stretching the neck muscles and plugging the ears with cotton wool or swimmers plugs.

**Candida or Yeast infections:** Tongue may have white or dark coating. Women may get vaginal yeast infections caused by candida overgrowth usually seen in Southern US due to high humidity. An infection on its own can cause a number of autoimmune type symptoms. Vinegar helps the most if taken one teaspoon twice a day. As well as yogurt and garlic three times a day, and honey in the morning. Reduction in the use of antibiotics also helps reduce yeast growth.

**Cold feet, Cold hands:** some people have cold proteins called, cold agglutinin or Raynaud's disease which will result in feeling of pain on exposure to cold. Use warm gloves along with Fish oil, aspirin or steroids. Keep yourself warm and hydrated, please read the Cryoglobulin chapter in blood disorders.

**Simple Blood tests to check inflammation:** We recommend that the **C.R.P.** (C reactive protein) and **Erythrocyte Sedimentation rate** (ESR) should be done in every individual. Simple blood test like the ESR is elevated in inflammatory disease. The C.R.P. is usually elevated in autoimmune diseases, normally the C-reactive protein should be zero. C.R.P is a more specific measure of inflammation and should be done in every individual to see whether inflammation is causing the disease. To check disease activity on a monthly basis only a E.S.R. needs to be repeated. Many cases will present with a normal ESR, even when the ESR is normal one should look at the history and clinical findings to properly diagnose the disease a underlying autoimmune disease process. Since the ESR has a tendency to increase with age a formula is used to calculate the true results. To calculate the normal ESR for the individual's age some doctors use this formula. Normal ESR: in men (man's age divided by 2) and in women (woman's age +10 divided by two).

**Simple Tests for immune deficiency:** Some people who develop autoimmune diseases may have immune deficiency. It is simple to diagnose these individuals. Diagnosis of immune deficiency is important because these individuals can easily be treated with I.V.I.G. Those individuals present with symptoms of fatigue or with frequent viral or bacterial infections like sinusitis, bronchitis, with frequent episodes of allergies. IgG or immunoglobulin-G is the most common antibody people have to help fight germs. Testing their **IgG levels**, **IgG Subclass levels** and **IgA level** is important. Usually the IgG subclass-2 or the IgG subclass-3 will be deficient in these people. The people with low IgG levels respond well to small doses of IVIg (intravenous immune globulin) at 400mg/kg per

month. In Celiac disease the IgG subclass 4 is usually elevated. The IgA levels are only elevated in Hench Schlein purpura.

**Screening Antibody tests for autoimmune disease:** Majority of the diseases will have some abnormal antibody associated with them. Not all the physicians agree on doing these antibody tests. The argument given is if you suspect an autoimmune disease then treat it with a test dose of steroids or I.V.I.G and if the individual responds you have a working diagnosis. Insurance requirements in USA require these tests results before they authorize treatment. For preliminary testing of autoimmune diseases the initial tests are **Rheumatoid factor, antinuclear antibody (A.N.A), anti-Thyroid Antibodies and Anticardiolipin Antibodies** (aCL antibody) .If an antibody test is slightly positive it should be considered diagnostic. Please see the managed care section at the end of this book which explains how to obtain approval of your treatments with the help of the above tests.

There are a lot of specific tests for autoimmune diseases. Like Infertility is associated with **Anticardiolipin Antibodies** (aCL antibody)in women and **antisperm antibodies** in men, Myasthenia is associated with **Acetylcholine receptor antibody** and in Multiple Sclerosis there is no associated antibody but is diagnosed by a Magnetic Resonance Imaging scan (M.R.I). The absence of antibody does not rule out the disease. A person can have Myasthenia and serum tests may still show that the Acetylcholine receptor antibody is negative. In thirty percent of the individuals with the disease there will be no antibody on their tests. This is called sero-negative disease. Coming back to M.S. even if the M.R.I. scan shows multiple white spots, other diseases like Celiac disease still need to be considered. Celiac disease is associated with **antgliadin antibody**, this can easily be tested to secure a diagnosis. It is important to do this as simple dietary restriction can change the persons life. More specific antibody tests are presented later with the individual diseases.

Most of the autoimmune diseases are diagnosed by history alone. Sometimes the diagnosed is suggested by elevated CRP or sedimentation rate. The rare diseases may need specific test like a MRI for Moyamoya (an inflammation of blood vessels in the brain).

**A trial for a Diagnosis:** If a individual has symptoms of fatigue, tiredness, weakness and other disorders like hypoendocrinism (hypothyroidism, hypocortisolism), hypovitaminosis, hypoaminoacidemia are objectively ruled out. Then it is best to try to get the diagnosis by a therapeutic trial of treatment. Try giving the affected person steroids and see if there is an improvement, the improvement suggests a autoimmune disease process.

**Chapter 4- Diet and Lifestyle changes for prevention of autoimmune disease:** The diet explained in this chapter is a anti-inflammatory diet that should be taken to avoid inflammation. Changes in diet alone help many diseases

Inflammation is caused by infections (Chlamydia, H pylori, Borrelia,), anger, chemicals, stress and mold (fungus). People exposed to chemicals and toxins (poisons) are at increased risk of inflammatory diseases (autoimmune). By decreasing inflammation one reduces the rate of disease and ageing, as inflammation is fueling stress, cancer, ageing, and allergies. Women get more inflammation in response to stress as compared to men.

The human body consists of many organs, brain, liver, bones, nerves, kidneys, eyes., there are many disease processes that affect these organs. The bottom line is inappropriate intake of food and supplements hurts the body more than helping it. Fats are good for brain functions and nerves, needed for digestion reducing the fats hurts the body more and even causes pre-mature heart attacks. Excessive intake of vitamins like B-6 can cause permanent heart disease. Alcohol intake causes neuronal damage. We need to adopt a diet which is balanced with a combination of carbohydrates, fats, proteins and fluids. Too much protein can cause attacks of gout and porphyria, too much carbohydrates can predispose to insulin resistance thus what we need is a balanced diet.

**Magnesium** is an important mineral for our bones, nerves and blood vessels. Found in green leafy vegetable salads, sesame seeds, pumpkin seeds, peanuts, halibut and black beans. Magnesium deficiency is involved in many conditions. These include migraine, multiple sclerosis, glaucoma, osteoporosis, Alzheimer's disease, muscle stiffness, pain, asthma, and fatigue. We recommend that everyone should take magnesium rich foods. If the medical problem only occurs at night, or in certain periods of the year like winter and autumn (minimum sunshine) then please try the magnesium supplement. Epilepsy or migraines which happen at night are relieved by magnesium supplements at 400 mg two or three times a day.

**Zinc** deficiency is a frequent human dietary problem in the United States and is associated with diseases like alcoholism, renal disorders, hair loss, skin lesions, gastrointestinal tract disorders, memory problems and asthma. Modest deficits in zinc cause reduced immune capacity and lower white cell counts. A suboptimal intake of zinc causes marked atrophy of the thymus, a reduction in leukocytes, and a reduction in immune functions. Zinc is needed for lymphocyte development and antibody production, particularly immunoglobulin-G. Zinc is contained in beef, yogurt, liver, whole wheat, sesame and pumpkin seeds. To maintain proper immune functions our body needs Zinc. High zinc intake may cause seizures.

**Silver** throughout history has been used as an antibacterial compound. The royalty in Europe used to eat from silver spoons and drink in silver cups due to which their skin color looked bluish (were referred to as blue blooded). The blue discoloration seen in the skin is due to excessive intake of silver a harmless condition called Agyria. The Food and Drug Administration today classifies colloidal silver as a pre-1938 drug. Robert O. Becker, M.D., author of *The Body Electric*, discovered that silver ions promote bone growth, improve immune function and kill surrounding bacteria. We would recommend drinking out of silver cups and using a silver spoon to eat or you can get supplemental silver.



**Aluminum** is toxic for humans; it has been associated with dementia. It is present in intravenous feedings called (TPN) and can cause seizures in infants. Avoid aluminum in buffered aspirin, anti-diarrhea products, cream filled cookies, baking powder and roll-on-deodorants. Please read the label of the product you are purchasing.

**Copper** deficiency is rare it will cause progressive symptoms, of weakness, fatigue, tiredness, alopecia, white hair growth, anemia, infections, constipation, neuropathy and difficulty walking. Copper serum levels are elevated up to threefold above normal with inflammations and with many chronic and infectious diseases, apparently because the body mobilises all tissue stores of copper to fight the condition. During remissions the copper levels return back to normal. Taking high dose of zinc creates a relative copper deficiency and helps to prevent formation of new blood vessels. Copper is available in a wide variety of foods, including fruits, nuts, legumes, avocados, and shellfish, but deficiencies may occur in adults who have celiac disease or are on very restrictive diets

**Fluoride** is toxic for all life forms a high dose will cause death. Milder doses in restaurants and schools have resulted in abdominal pains. Chronic low doses will stunt growth and have resulted in hypothyroidism. It's recommended that you drink the non fluoride water. Finland, Sweden and Holland have cut tooth decay rates by 90%, 80% and 70% respectively over the past 20 years, without using Fluoride in their water supply. A scientific study showed people taking fluoride in the water had lower amount of infection fighting cells. Trees do not grow well with fluoride in the water and to compensate trees will produce more magnesium to trap the fluoride. Toothpaste, pesticides, automotive wheel cleaners all can contain fluoride. Ingestion may cause low calcium in the blood, epilepsy, irregular heart beats, and coma. In hospitals calcium chloride and magnesium salts are given to reverse fluoride intoxication. Do not leave fluoride products within the reach of children. (Read the labels).

Avoid Dental amalgam (an alloy made of silver, copper, tin and zinc, bound by elemental **mercury**). If you cannot get an amalgam free cavity filling can say goodbye to the tooth. Some of the dental amalgams contained mercury. The use of mercury was related to development of Multiple Sclerosis. You can use cilantro, which chelates mercury out of your body within a week.

Some of the treatments to avoid are **Ayurvedic medications** which contain herbs, minerals, metals, or animal products and are made in standardized and nonstandardized formulations. During 2000-2003, a total of 12 cases of lead poisoning among adults in five states associated with ayurvedic medications or remedies were reported to CDC. Cases have been reported all over the world and some users died.

Hydrogen peroxide bought from health food stores in the US and ingested resulted in instant strokes, facial burns and skin burns. Hydrogen peroxide should not be ingested. The individuals were trying to use the supplement to improve their oxygen levels.

People with **porphyria** usually have darker urine color if left in sunlight. These people should only use **high carbohydrate** diets and avoid alcohol and high proteins. People with gout should also avoid high protein and alcohol in their diet.

**Fats & Oil:** Fats and oils are important for the body especially for the brain and nerves. Myelin is made from lipids, enzymes and body functions are related to amount of lipids in the body. Higher intake of oils containing omega-3 will lower cholesterol. We have seen many young doctors die from fatal arrhythmias caused by low fat diet and heavy exercise. Low fat diet causes athletes to develop cardiac arrhythmias.

**If you have Celiac or Autoimmune diseases try Gluten free diet,** should be tried by those who have weight gain, temper problems or autoimmune diseases. The diet is simple; Use only milk, rice, vegetables, corn, fruits, meats, fish, chicken, honey, juices and water. See how you feel? No pasta, no beer, no alcohol, no bread, cakes or cookies. The cornbread, corn flour is perfectly ok to eat with a gluten free diet. The grains not allowed are wheat, rye, millet, barley, and oats. At least for three months the above diet should be tried to see if it helps you. Some people do well on a lactovegetarian diet (a diet of milk, vegetables and fruits).

Children and adults who snack frequently on high carbohydrate foods may develop, "auto-brewery syndrome". These individuals may have short intestines to begin with, they show features of alcohol intoxication because of abnormal yeast proliferation after ingesting carbohydrate-rich meals. Blood test on a person who had no external alcohol, showed a ethanol concentration of 15-mmol. These people have a tendency to fall asleep after a heavy meal, due to the production of large amount of alcohol from the fermentation in the autogenous brewery. Treatment is simple start fasting and take low carbohydrate foods.

**Organic Foods:** One should eat organic food and avoid processed food. Naturally grown food will not contain the poisonous pesticides present in non organic grown foods.

Breakfast consisting of oatmeal with milk is recommended along with teaspoon of organic honey, a tea spoon of olive oil. Alternate with a fried egg, which means a full egg the main nutrients in an egg are found in the yellow portion, the white portion is full of protein called albumin. Take some blue berries, walnuts and almonds. A slice of toast made from full grain bread. (**Avoid white bread**). Avoid **white sugar and candy**. Brown sugar is much better than white. Tea has antioxidants and taken three times a day is very beneficial for health. Coffee causes too much stimulation and some people may see symptoms of fatigue. Green tea is more healthy and taken four times a day will keep you healthy and reduce inflammation. Many studies have shown that green tea drinkers have a lower incidence of stomach cancer because it gets rid of *h pylori* from the stomach. Yogurt or milk taken three times a day regularly will help get rid of *h pylori*. A small portion can be taken after the main breakfast. Breakfast is the most important meal of the day so do not skip it.

Snacks between meals should consist of fruits and **nuts, apples** and water. Those of you who are going to do extreme exercise they need to take a high load of **carbohydrates**

before the activity. Athletes should also take a normal amount of **fat** as a low fat diet predisposes them to immune dysfunction. More fat in the diet helps the body in providing readily available energy. Otherwise the body has to turn into anaerobic mode does not sound good. Lunch should consist of high vegetables & low protein diet (chicken, Fish, and well cooked beef). Eat plenty of fruits, carbohydrates and replenish your fluids by drinking water. The best lunch will be green salad mixed with fruits and nuts with a dressing of **vinegar** and olive oil. Men need to avoid Tofu (tends to increase feminine hormones). Regular use of at least **two tea spoons of vinegar** will clear all fungal infections in the body. The nail and skin fungus will come back within one week of stopping vinegar. Carbohydrates following lunch are ok.

For dinner again eat a high vegetables & low protein diet (Chicken, fish, well cooked) with vegetables, fruit and water is recommended. Remember to use full grain bread. Instead use fruits. The best dinner will be green salad mixed with fruits and nuts with a dressing of vinegar and olive oil.

**AVOID PORK! (All the countries that got SARS were those who consumed Pork, countries where Pork was not eaten did not get SARS).** Please visit the farms in North Carolina to see how they raise them.

Chew your food well, chewing food in the mouth will allow more absorption of vitamins from the sublingual area. **Eat slowly** and chew food to small particles before **swallowing**. This helps avoid choking. **Don't drink and breathe at the same time**. This will put enough fluid in the wrong pipe to give you a scare and tears.

We also recommend eating brown rice. The polished white rice has the bran coating removed and has lost most of its nutrients (thiamine). Basmati rice has low carbohydrate value and is recommended. Whole wheat bread is the best, all the nutrients and fibers are in the husk. People who eat white bread develop magnesium deficiency which leads to obesity and inflammation.

Avoid sweeteners :(Sweeteners can cause seizures, fatigue and headaches). In only the sensitive people seizures have been caused by a sweetener it is not a risk for 99% of the population. In some other sweetener has relived their joint pains.

**All the vitamins and supplements are found in food.** Thus we recommend that you get your vitamins from fruit, milk, honey and vegetables. The most common vitamin deficiency seen in clinical practice is **B12**. If you have tingling numbness or weakness your doctor may check the B12 level in you. If the level is low they will prescribe you a B12 injection. The alternative is sublingual B12. Most individuals with B12 deficiency on testing show a normal B12 level. There are some people who need vitamin supplements, those who have damaged stomach lining. There is increased risk of stroke, heart attack, epilepsy, headaches if homocysteine levels are elevated or increased serum concentration of total homocysteine. Treatment with several B group vitamins (**B12-B6 -Folic acid**) has been shown to reduce the level of homocysteine in the blood; even in persons whose serum levels of these vitamins is in the range currently considered normal. For better absorption a

sublingual form of the vitamins is recommended. In place of multivitamins we recommend a teaspoon full of honey (organic), regular milk, fruits and vegetables.

**Majority of studies have show that more people die from excess vitamins and not from deficiency.** So avoid popping multiple vitamin pills daily. For those who insist on a multivitamin **just take one multivitamin a day**, in young people toxicity has developed from just one multi-vitamin a day. Some people self prescribe B6 for their neuropathy. This may lead to excessive high levels of B6 in your body and result in a permanent neuropathy. It is recommended to get your vitamin B6 and homocysteine level checked once a year.

**No processed meats like, (hotdog, sausage, salami or pastrami). Processed meats increase the incidence of cancer.** Nature created all the foods with a proper balance of minerals, fats, proteins, carbohydrates and vitamins. Processing of foods disturbs the natural balance of the meals.

**Fluids:** Start your day in the morning with a glass of water. Life on Earth will not be possible without water. Drinks a total of 8 glasses of water a day, (Iced tea, water, lemonade, tea, milk). Regular fluid intake increases the motility time of the stomach and intestines, washing the bacteria away. This results in getting rid of constipation, hemorrhoids, dizziness, muscle and weakness. Taking care of fluids will avoid kidney stones, keep your teeth clean, avoid fatigue and reduce blood clots. Proper fluid intake will help you lose weight as you will not feel hungry. Some constipated people have held 40lbs of fecal material in their guts. Milk is a very important fluid. Daily intake of milk or yogurt has been associated with low incidence of *H. pylori* a bug that induces many of the autoimmune diseases. Milk should be consumed as a whole product no one should be using low fat milk. Green tea also inhibits *H. pylori* in the stomach.

**Soda** has acid which increase the risk of tooth decay. The sugar and acid will damage the enamel especially in children. Organic milk is the best drink as it does not have growth hormone and pesticides.

**Beer** has been shown to be toxic to the brain, nerves and muscles. Vinegar provides all the benefits of improving blood flow similar to alcohol but without the hangover. Alcohol causes nerve damage (neuropathy), muscle damage (myopathy) and liver toxicity. Scientists have reported that a single glass of beer is able to destroy millions of neurons. Those individuals who are suffering form mold related issues need to pay attention to the fact that darker the beer means higher the mold content.

**Breathing & Atmosphere:** The best drug on Earth is **Oxygen**. It is considered a drug in the US and thus requires a doctor's prescription to be dispensed. **We cannot survive a millisecond without oxygen.** So breathe as much as you can, deep breathing every morning will get you going. Try to live close to **sea level** as the atmospheric pressure is higher. (No prescription no pharmacy involved). If you live at sea level and decide to visit the mountains **do not go hiking on the first day**. It takes time for your body to produce more red cells. If you have cardiac or autoimmune-disease then avoid **high altitude**.

On conservative estimates we breathe **21, 600 Liters** a day. Every filter need to be cleaned. For a huge body we carry a small filter in the nose, we need to clean this at least once a day. More oxygen kills *Borrelia* the cause of Lyme disease. Remember to take deep breaths, this helps burn calories. Studies show that oxygen concentration has decreased. Some of the planets mass extinctions of dinosaurs occurred during or after geologically sudden drops in atmospheric oxygen. The atmospheric concentration of oxygen then probably was about 35 percent; the current oxygen concentration is 21 percent.

Half of the world's oxygen is produced via phytoplankton photosynthesis. The other half is produced via photosynthesis on land by trees, shrubs, and grasses. The concentration of oxygen in the air is the same at all altitudes, but atmospheric pressure which determines how much air enters the lungs with each breath does decrease with altitude. As less air enters the lungs, the body tries to compensate by breathing faster and deeper. This begins a chain of reactions that can result in altitude sickness. A simple way to recover from this is to breathe faster at high altitudes.

When a storm is approaching and the Barometer falls, that affects the amount of oxygen entering our lungs. Slightly less oxygen combined with increased swelling in the body, produced by the falling barometer results in a feeling of stiffness and pain, felt by people with autoimmune muscle and nerve problems. Lower atmospheric pressure makes our body swell up, causes a uncomfortable feeling to individuals with Fibromyalgia and migraine.

Carbon dioxide levels are now 35 percent higher than at any point in the last 650,000 years. There is a higher concentration of Carbon Dioxide under a tree at night. (A location to avoid at night and do not sleep there). The rising levels have led to a near doubling of dissolved organic carbon, (DOC), in rivers over the past 15 years. When DOC reacts with the chlorine used to disinfect supplies, it forms chemicals such as trihalomethane and haloacetic acids that have been linked to bladder cancer, stillbirths and birth defects. You need to avoid any chemical in your water. Water Filters are a necessity.

Approximately 14 million U.S. adults and 9 million children have asthma, according to 2001 CDC figures. Childhood asthma rates have more than doubled in the U.S.A., since 1984 in a trend that has largely baffled scientists. Atmospheric carbon dioxide (CO<sub>2</sub>) may be the main culprit. Recent studies identified CO<sub>2</sub> levels in large U.S. cities including Phoenix and Baltimore, which are at times up to 60% higher than in rural areas. A recent study suggested that ragweed, is responding to the higher CO<sub>2</sub> levels in the atmosphere by producing more pollen. Need to avoid congested poorly ventilated buildings where CO<sub>2</sub> levels are even higher. "Ragweed grew faster, flowered earlier and produced significantly greater ragweed pollen at urban locations than at rural locations,"

**Exercise:** The best exercise for someone who has Polyneuropathy (numb feet) is to use the stationary Bike or simply the exercise pedals which you can place next to your favorite couch. Use them for 10 minutes at a time four times a day. This will reduce pain, improve strength by improving the blood circulation. Best of all it can be done in the security of your environment. The next best thing is walking and if extremes of temperature bother

you use the local mall. **Remember the Brain, nerves and body can only consume carbohydrates for fuel** so pure protein diets may drop some IQ points and causes Gout.

**Stretch:** Before you get out of bed, stretch like a cat. This will lessen the stiffness in the joints when you start walking. Stretching should be done all along the day. People who stop stretching tend to develop osteoporosis. Remember to change your position and stretch regularly. Stretching exercises are recommended about five times a day. These will help reduce stiffness. Turn your neck from side to side, Bend down on the hips and place your hands on your knees. Bend down to touch the floor. Remember to stretch at least five times a day.

**Avoid sitting in front of a cold draft.** Cool air makes you stiff. New Born babies will cry if they are not wrapped due to a feeling of coldness. If the person has thiamine deficiency then a cold draft will make their symptoms worse.

**Smoking:** Chronic heavy smoking can reduce blood flow to your vital organs, (Brain). **The Surgeon General has shown that smoking causes lung cancer.** Smokers have lower incidence of some autoimmune diseases including Alzheimer's and Parkinson's. This is thought to be due to Nicotine, and the same benefit is seen in tea and coffee drinkers. Get the beneficial effects by tea and coffee. **4000 Americans die, per year, of lung cancer and 37,000 due to heart disease, caused by other people's passive smoke.** Smoking from a water pipe carries the same risk as from other sources. (Waterpipe, "shisha", "hookah", "hubble bubble") Smoking has been shown to reduce the incidence of Parkinsonism in several studies.

While driving in heavy traffic try recirculation of cabins internal air, to avoid inhaling the fumes of Trunkers. **The best air in New York is on the day the buses go on strike.** Higher indoor air pollution happens in homes with coal burning and open fireplace than in homes with central heating. Do not place humidifiers in a infants room, they have been associated with induction of (Kawasaki's disease). Do not use chemicals to clean the carpet, use hot water instead. Even a small spray of carpet cleaner has caused (Kawasaki disease) in infants. Water is a universal cleaner just boil it to clean any carpet stain.

**Clothing:** Do not wear synthetic clothing, cotton keeps you feeling healthy. (Silk underwear's may cause infections). Do not use sun glasses early in the morning. That reduces your melatonin production as well as Thymosin. This may end up causing you to be fatigued later in the day.

**Personnel hygiene:** Do not forget personnel hygiene. Take a bath everyday with soap to wash off the bacteria. Brush your teeth twice a day minimum, use dental floss or Colostrum to clean plaque, and wash your mouth five times a day with water to get rid of bacteria. The biggest cause of Heart disease is the bacteria which enter from your mouth directly in your blood stream. Honey prevents gingivitis and periodontal disease, taken three times a day after meals. Wash your hands at least before every meal. Wash and clean the nose minimum five times a day so clean air can enter your body, remember the nose is a filter and not an object for plastic reconstruction. Wash the fruit you buy and keep your house

clean. Make sure the bed sheets are clean. No bad odors should come from you, your clothes or your home. Bad odors suggest mold, bacteria or toxins. (Clean) Good smells improve health (aromatherapy) works so use perfumes around the house. Make sure you wash your hand all the time you cannot afford another infection.

**Spirituality & soul:** Spirituality is one mechanism that people with disease can utilize in order to achieve control over the disease as well as reducing stress and achieving inner peace an underlying premise being that taking care of the soul is a necessary element in healing the body. When we load software on a computer suddenly it comes alive. Without software a computer has no soul its dead.

Help your soul get stronger by meditating, praying and focus on telling yourself that you are improving daily. If you think positively, keep a smile on your face and walk with energy. Things around you will change. If there is too much stress at work then start talking to others so you do not have to pay to the psychiatrist. Exercise which involves stretching will help in overcoming stress too. Think about having a disease free future. Travel and enjoy life. These changes will work no ifs ands or buts about these. While you meditate your soul relaxes. Think about a solution, when a problem arises. Soul needs a reason to live on that is love. (Love someone, something and see what it will do to you). You need to have a **purpose**, a **project** need to involve yourself in something. Try to help other people, you receive an automatic reward which makes you feel good and relaxed.

Finally we are but a projection of our conscious. Some can control the environment around us. Some can look in the future. There is a lot more to learn about ESP or the sixth sense, and then we know. The best person is instinctive, if your brain raises red flags on what you are doing pay attention change course. (This is a form of ESP message and not a seizure). Remember not to get upset from the news. Do not let adversity bother you, learn to forgive, forget and relax. Stay calm ignore others attitudes. One needs to learn to accept fault no matter how minor. When any one offers criticism take it positively. Learn, Improve and Excel. (Perseverance command success).

Doing negative things, (Hate, Rage, reduces tolerance), depresses the immune functions, raises inflammation. Helping people automatically gives you satisfaction. Helps boost your immune function, reduces stress. When you talk negatively about others or do negative criticism your body may suffer more inflammation as it makes you angry. So tolerate, this attitude will let you live longer and healthier.

All the worldly goods are left back even the body stays in the grave. Your soul will be with you forever. (**All the hidden treasures of the Pharos were stolen by 1000BC.**)

Medical research has shown that prayer and mediation makes beneficial changes in your body. Enjoy your partner; bring the positive out of them. Enjoy your work, focus on the positive and suppress the negative. You should be the last person to consider surgical treatment of any organ for pain relief. Most of the autoimmune diseases can be taken care of without surgery (fully explained in the handbook of autoimmune diseases). This includes

herniated discs in the back and neck, aneurysms, prostate problems, chronic pelvic pain and pancreatitis.

**Fasting: Benjamin Franklin** - "The best of all medicines are rest and fasting"

Fasting is the world's most ancient and natural healing mechanism. Fasting triggers a truly wondrous cleansing process that reaches right down to each and every cell and tissue in the body. The entire alimentary canal is swept clean. By rebuilding immunity, health is naturally restored and disease disappears. Fasting promotes cleansing and healing; helps normalize weight, blood pressure, cholesterol; rebuilds the immune system; and helps reverse the aging process. If we are to get these poisons out of our bodies we must fast. By fasting we give our bodies a physiological rest.

Fasting is abstinence from all food and drink for a limited period of time to maintain or improve health, or treat a specific illness. Most of the research into the therapeutic value of fasting has explored the water only method, can drink water but abstaining from all food. A short fast, lasting from one day can generally be tolerated by most people. An extended fast up to three days is not recommended. Fasting has been known since ancient times. There are references to it in the Bible, Koran, ancient Chinese, Greek medical texts state:

"does well unto himself thereby; for to fast is to do good unto yourselves - if you but knew it."

"but he from among you who is ill or suffers from an ailment of the head shall redeem himself by fasting".

People of all religions have fasted as part of religious rituals well known is the Muslims Ramadan. Fasting to benefit health is an old practice and is generally practiced today only in prosperous Western societies. The Natural Hygiene system practice was started by Isaac Jennings, M.D. a Yale graduate who rejected the therapeutic use of drugs to treat specific ailments and instead developed a treatment program that included periodic fasting, a vegetarian diet, pure water, sunshine, clean air, exercise, and rest.

"Instead of using medicine rather fast a day." Avicenna, the great Arab physician often prescribed fasting for three weeks or more. It is claimed that, as a result of fasting, people often recover from arthritis, asthma, digestive problems, high blood pressure, heart problems, and many other diseases. Fasting means eating nothing, drinking only water and getting lots of rest. Autolysis or self-digestion is a state the body enters about the fourth day of a fast; according to Dr Herbert Shelton, in this state the body can break down even cancerous tissues and eliminate them.

Recent research shows skipping meals may be good for you. It has been known for years that sharply restricting the calorie intake of laboratory animals increases their life span. But a new study by researchers from the National Institute on Aging found that mice that fasted every other day, and then were allowed to eat what they wanted on the intervening days, seemed more resistant to diabetes than did control mice or animals on calorie-restricted diets. They were also resistant to a condition similar to



Alzheimer's disease. In addition, the intermittently fasting mice produce more of a chemical called brain-derived neurotrophic factor (BDNF), which promotes learning, memory and the growth and survival of nerve cells. This BDNF appears to make the animals more resistant to a neurotoxin that produces brain damage similar to Alzheimer's disease. The intermittently fasting animals cells also become more adept at scavenging glucose from blood. That is an anti diabetic effect, detectable on glucose tolerance tests.

In a trial of 16 individuals with classical rheumatoid arthritis (RA) underwent fasting for ten days, followed by a nine week period on a lacto vegetarian (milk, vegetarian diet). After fasting, 5 of 15 individuals showed objective signs of improvement. **The fasting individuals showed reduction in all of the following, pain, stiffness, consumption of analgesics, and serum concentration of orosomucoid** (a protein found in blood plasma, an indicator of inflammation). **Study concluded that fasting may produce subjective and objective improvements in RA.**

Fasting is recommended for those individuals who are not doing well. Studies have shown fasting reduces inflammation in rheumatoid arthritis and helps individuals with Fibromyalgia. The simple fasting can be done by not eating anything from morning to evening; you can have water within that period. Doctors have known that **fasting can cause attacks of acute intermittent porphyria**, and that a high-carbohydrate diet can help relieve the attacks.

**Spices:** Things like ginger, garlic, turmeric, cloves, black seed, cilantro, saffron, and cinnamon are all neuron protective, demonstrate anticancer activity and get rid of over a hundred infections. Spices should be included in every diet. UCLA's Alzheimer's disease Research Center found that curcumin has one additional property not shared by most spices. It directly inhibits the production of amyloid plaques, the sticky substances that directly causes Alzheimer's disease. Turmeric, in fact, seems to cut the number of amyloid plaques in half. Embracing a cuisine rich in spice, as well as in fruit and vegetables, may further enhance the chemopreventive capacity of one's diet. Spice up your life, with extra spices in your food. All the spices have been show to reduce inflammation and enhance the immune system.

From 1991 -1993 a epidemic of optic and peripheral neuropathy affected more than 50,000 people in Cuba. With loss of vision, diminished color vision, optic-nerve pallor, and decreased sensitivity to vibration and temperature in the legs of affected people, was seen. Tobacco use, particularly cigar smoking and poor nutrition was associated with an increased risk of optic neuropathy. The number of new cases decreased after the initiation of vitamin supplementation in the population. The risk was reduced among subjects with higher dietary intakes of methionine, vitamin B<sub>12</sub>, riboflavin, and niacin and higher serum concentrations of antioxidant carotenoids.

Except for the USA bitter almonds are sold all over the world. California's trees are of the sweet-almond variety Sale of bitter almonds is illleal in the USA. Bitter almonds contain a small quantity of a substance that, in the presence of water, forms deadly prussic acid. This substance is also present in the kernels of prunes, peaches and apricots - other fruit trees

that, like the almond, belong to the rose family. Heat destroys the poison, so cooking renders it harmless. Children are at high risk after eating bitter almonds.

Cassava is the third-most important food source in tropical countries, but it has one major problem: The roots and leaves of poorly processed cassava plants contain a substance that, when eaten, can trigger the production of cyanide. Cassava has caused spastic paralysis and optic atrophy in Nigeria.

Eat a balanced diet, rotating different foods which include, vegetables, spices, carbohydrates, oils, excess of any single food can lead to toxicity.

## **Chapter 5- Immune System**

The immune system acts as a double edged sword, it defends against microorganisms and toxins. Sometimes the immune system mistakenly will attack the persons own body (Friendly Fire). At the heart of the immune response is the ability to distinguish between self and non-self. Every body cell carries distinctive molecules that distinguish it as "self." Normally the body's defenses do not attack tissues that carry a self marker.

The organs of the immune system, positioned throughout the body, are called lymphoid organs. The word "lymph" in Greek means a pure, clear stream. Lymph nodes are small, bean-shaped structures that are laced throughout the body along the lymphatic routes. Lymph nodes contain specialized compartments where immune cells congregate, and where they can encounter antigens. Thymus located in the neck makes T-cells, they are only released in the bloodstream after being tested in the thymus that they will not attack their own body cells. In autoimmune diseases something goes wrong in the thymus. Removing part of the abnormal thymus helps some autoimmune diseases. Spleen is a large organ which helps get rid of cells tagged by antibodies. Tonsils are one of the primary sites of the immune system which encounters bacteria and triggers a immune response.

The attacking cells in the immune system are of two types called leukocytes:

- The **phagocytes** cells are the policemen that take out the bad guys.
- The **lymphocytes** cells are the learning cells which remember the bad guys.

The most common phagocyte is the Neutrophils which fights bacteria. In a bacterial infection, the number of neutrophils increases.

All of the immune cells originate from the stem cell in the bone marrow. In autoimmune and immune deficiency diseases replacing the stem cell provides a new immune system.

Lymphocytes are of two types, **B-lymphocytes** and **T lymphocytes**. Lymphocytes come from bone marrow and mature into B cells, others develop in the thymus gland into T-cells. **B-lymphocytes** are the **Bodyguards**, which look for invaders and make specific antibodies against them. **T-cells** act like **Tanks**, who destroy the invaders identified by the B cell.

A foreign substance invading the body is an **antigen** example (body parts of h. pylori, mycoplasma). On detection of an antigen, immune cells work together to recognize and respond to it. These cells send messages to the B-lymphocytes to produce antibodies. Antibodies are specialized Y shaped proteins that lock onto specific antigens. Antibodies and antigens attach together, like a key and a lock. In a disease, the T lymphocyte is responsible for not attacking the body. In autoimmune disease the T cell is deceived into attacking the body by a process called molecular mimicry.

Once the B-lymphocytes has produced antibodies, these antibodies then exist in a persons body. If the same antigen is presented again, the antibodies are already there to do their job. If we get measles once, then you do not get them again, as you have the antibodies. Immunization is used to prevent diseases by an attenuated antigen produce antibodies for protection, thus an attack by the real germ should have no effect. B cells make the following types of antibodies, (IgA, IgG, IgM, IgE, and IgD). IgG is the most important type and helps us fight infections; this has four sub types called (IgG subclass 1-4).

Antibodies can find an antigen and attach to it, to destroy antigens tagged by antibodies is the job of the T-cell. In an infection an antibody will attach to the bacteria and then comes the phagocyte to eat them up. A sub type of the T-cell is called Natural-Killer T-cells (NKT), they are the immune systems emergency reponce team to find and destroy bacteria and cancer cells. There are other types of T-cells, called helper, suppressor and cytotoxic. Cytokines are chemical messengers which are the chief tool of T-cells. Lymphocytes, including both T-cells and B-cells, secrete lymphokines, while monocytes and macrophages secrete monokines. Cytokines recruit many other cells and substances to the field of action. Cytokines encourage cell growth, promote cell activation, direct inflammatory traffic, and destroy target cells including cancer.

Antibodies produced by B-cells can neutralize toxins (poisonous or damaging substances) produced by different organisms. Lastly, antibodies can activate a group of proteins called **complement** that are also part of the immune system. Complement assists in killing bacteria, viruses, or infected cells by destroying the cell walls. *N meningitides* infections and SLE, glomerulonephritis, arthralgia, uveitis are commonly seen in complement deficiency. Complement is activated and increases in heart attack individuals after streptokinase is given, but responds to a high dose of magnesium sulphate. The immune

system protects the body against cancer and disease. This protection is called immunity. Humans have three types of immunity - innate, adaptive, and passive.

**Innate Immunity:** Innate immunity provides a swift response against infectious agents prior to the initiation of adaptive immune responses. Cells involved in innate immune responses include macrophages, neutrophils, eosinophils, and natural killer T (NKT) cells.

**Adaptive Immunity:** A slower response by lymphocytes, developed by repeated exposure to infections and vaccination. The lymphocytes are learning cells, they remember the attackers and send out T-cells, to hunt the attacking cells.

**Passive Immunity:** This is a temporary immunity provided to the body, which is removed in a month. Antibodies in a mother's milk (colostrum) provide an infant with temporary immunity to diseases, that the mother has been exposed to. This can help protect the infant against infection during the early months of childhood. When IVIg is given it offers protection for 4 weeks

As a person gets older, they usually become immune to more germs, through repeated exposures. Adults get fewer colds than children, adult bodies have learned to recognize and immediately attack many of the viruses that cause colds and flu.

**Heat shock proteins (HSP)**, also named *stress proteins*, these proteins are present in all cells of all life forms. They are formed when a cell is exposed to environmental stresses like heat, cold and oxygen deprivation. *HSP* are present in cells under normal conditions. Abnormal peptides that are found only in sick cells need to be moved to outside the cell's surface. Inside the cell, heat shock proteins take these peptides (antigens) and hand them over to other molecules. The immune system sees these peptides as red flags, which will trigger an immune response. These abnormal peptides are called antigens a term that describes any substance capable of triggering an immune response. If a normal cell dies in scientific terms this is called (apoptosis) no *HSP* are produced and no inflammation results. The normal death of cells is also called programmed death, which does not trigger inflammation. Cells under stress will start producing *stress proteins*, which start getting the immune system's attention and these results in inflammation.

### **The Immune System Disorders.**

- Immunodeficiency disorders ( if we have reduced immunoglobulins or antibodies)
- Autoimmune disorders (in which the body's immune system attacks its own tissue)
- Allergic disorders (the immune system reacts in response to an antigen, its an immediate reaction which can cause death. Epinephrine is used to turn it off)

We have some important Y shaped antibodies, one is called the antiidotype antibody, and they can attach to many different types of antigens and inactivate them. Some people who get autoimmune diseases have less of these antibodies. Some other antibodies are called the

autoantibodies these tend to attack our own body cells. In autoimmune diseases autoantibodies are increased.

To keep our immune system healthy we need to keep our body clean. Wash our hands and mouth five to six times a day. Learn to meditate and slow down the pace of our work. Learn to drink more water and eat mainly vegetables and fruits, to help keep the inflammation at low levels.

-Chapter 6 what are some Neurological Autoimmune Disorders.

### Acute Disseminated Encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) is an autoimmune disorder characterized by inflammation of the brain and spinal cord caused by damage to the myelin sheath. The myelin sheath is the fatty covering, which acts as an insulator, on nerve fibers in the brain. ADEM may occur in association with a viral or bacterial infection, as a complication of vaccination, or without a preceding cause. The numbers of children developing this condition are increasing 0.4/100,000/year; the incidence quadrupled during 1998-2000.

**Symptoms:** Onset of the disorder is sudden in a child following flu like illness or vaccination. The person starts to develop headaches, aches and pains, followed by confusion and may become comatose. Symptoms vary among individuals, headache, vomiting, tiredness, confusion, fever, difficulty walking, stiff neck, vision loss, weakness in the legs, coma, and seizures may be seen.. The disorder occurs in children more often than in adults. Some may mistakenly call this Multiple Sclerosis however Multiple Sclerosis does not present with fever. Some individuals present with weakness on side of the body they usually have a Mycoplasma infection. Jerking of arms due to Myoclonic seizures can be seen. Rarely children may become confused and be misdiagnosed as psychosis. Some children may develop double vision due to brainstem involvement and this may be the first symptom of A.D.E.M.

**Tests:** Anti-Streptolysin-O titer (ASO) needs to be obtained which is usually elevated, and throat cultures for streptococcal infection and Chlamydia are obtained. Magnetic resonance imaging (MRI) scan of the brain usually shows multiple white spots, rarely some blood may be seen and tumor like lesions are also seen. Spinal tap can be done to look for raised levels of inflammatory cells, and to look for an inflammation marker called oligoclonal bands which are absent in ADEM. (Oligoclonal band are associated with Multiple Sclerosis). The spinal fluid protein is usually elevated. **Herpes encephalitis** needs to be ruled out in individuals with Herpes the CSF chemistry is as follows, cell count is usually 100 WBC and A few hundred red cells, glucose is normal with MRI showing bilateral or unilateral temporal lesions. Vitamin levels for B-6(pyridoxine), B-12(cynocobalamin), Thiamine need to be checked with serum homocysteine levels.

**Treatment of ADEM:**

- Group beta hemolytic streptococcal bacteria are usually the cause confirmed by elevated ASO titers, and then treatment with penicillin is started. ADEM has also been reported to be caused by Chlamydia pneumoniae infection. The diagnosis is established by a checking a tracheal swab for increasing titres of Chlamydia-IgM antibody. The individual can be treated with **doxycycline** and **prednisone** and recovery is usually complete. Other antibiotics like, ciprofloxacin, chloramphenicol or azithromycin are appropriate under most circumstances.
- In all cases weather the ADEM is caused by vaccination or an unknown infection the individuals needs to be given steroids or IVIg plus doxycycline. To help control inflammation Steroids work 90% of the time and in the resistant 10% case IVIg can be used 500mg/kg/day for 4 days. Rarely plasmapheresis or cytotoxic drugs can be given in resistant cases.
- Treatment of herpes encephalitis is **Acyclovir 10mg/kg q8h iv (30mg/kg/day), infuse each dose over 1 hour, treat for 10-14 days.**
- If vitamin levels are low then replacement is required.

In some cases complete resolution is noted within a few days, but more frequently occurs over the course of weeks or months. About 5-10% of the cases may go on to develop M.S, so we recommend a good diet with fish and omega-3 to reduce inflammation.

**Autoimmune Epilepsy: Think Autoimmune Epilepsy, in epilepsy which does not respond to current anti epilepsy medications (Refractory individuals and Myoclonic epilepsy):** Epilepsy is a symptom of many neurological disorders and in the past an etiological explanation could not be identified. There is evidence that autoimmune mechanisms have a role in causing epilepsy. Autoimmune epilepsy is commonly associated with Myoclonic photosensitive epilepsy. Just like any autoimmune disorder the symptoms of epilepsy are remitting and relapsing. Epilepsy is associated with injury, surgery, vaccination, infection and often seen in individuals suffering from other autoimmune disorders. Numerous publications have shown an association of serum auto-antibodies in individuals with epilepsy syndromes, which responded to immunomodulation treatment. Following a generalized seizure increased white cells, proteins, elevated CRP and increased levels of interleukin-6 (IL-6) are seen in individuals with recent tonic-clonic seizure. This suggests the involvement of inflammation with epilepsy is even more common then what we think.

In our own experience we have seen a close association of autoimmune epilepsy with sleep deprivation, in young individuals. Many of the individuals, who had been called intractable epilepsy for years, were simply controlled by drug manipulation. Autoimmune epilepsy is seen frequently with thyroid disorders, SLE (Lupus), Sjogrens or arthritis and antiphospholipid disorder, if they get a seizure it is more likely related to a autoimmune

process. The autoimmune epilepsy starts suddenly and appears unresponsive to medical treatment (refractory). Later a pattern of remission and relapses is seen. Light sensitive individuals, with light induced seizures, and those who have seizures at night are more likely to have autoimmune epilepsy.

In women and young men new onset of epilepsy can be worked up by checking antibodies for, antiphospholipid antibodies, antinuclear antibody, and glutamic acid decarboxylase (GAD) antibody. The GAD antibodies are higher in diabetics with associated epilepsy. Thyroid antibodies and thyroid functions need to be checked in all individuals. If a SLE individual gets epilepsy then common sense needs to be used to think about an autoimmune cause. If screening is positive for antibodies then immunomodulatory treatments is to be considered. If a individual is not responding to epilepsy medication it is worthwhile to start them on a short trail of steroid and see if the seizures respond and the brain lesions disappear.

One to five percent of the epilepsy individuals may have celiac disease. These individuals also do not respond to epilepsy medications and they have unexplained weight loss. Anti Gliadin antibody can be positive. Every individual needs to try the fruit vegetable, protein, rice and milk diet which is free of wheat, rye, barley, millets and oats for four months. No beer or alcoholic dinks allowed. Within that period if a benefit is seen then the diet should be continued. These individuals may show dramatic calcifications (bone like lesions in the brain) in the occipital (back of the brain) regions of the brain. We do not recommend mass screening for Celiac Disease instead, increased alertness should be observed in individuals at risk of the condition. People with celiac disease also have abnormal thyroid function tests, may have diabetes and serum Carnitine deficiency.

Below is a description of some epilepsy syndromes:

### **Landau-Kleffner syndrome (LKS), known as acquired epileptiform aphasia**

Landau-Kleffner syndrome (LKS), or acquired epileptiform aphasia. It is an autoimmune childhood disorder characterized by deterioration in language skills in association with seizures or seizure activity on the E.E.G. The disorder affects children, between the ages of 3 and 8 years.

**Symptoms:** The children usually experience an abrupt loss of language and comprehension and a reduction in their ability to express themselves. A child who starts to stutter with their, this can be an early presentation of LKS. Approximately 70-80% of children with LKS have seizures; however, the presence of seizures is not a requirement for a diagnosis. There is usually a small improvement seen between attacks of LKS, just like any autoimmune disease.

**Tests:** With modern PET scanning the area affected by LKS is in the left temporal Lobe of the brain, a region next to the left ear. This area in the brain is responsible for human

speech and hearing sounds. The **EEG** recorded during sleep is diagnostic and shows focal and multifocal spikes and spike wave discharges predominantly in the temporal and parietal regions. In many cases onset can be temporally related to a previous infection.

Autoantibodies directed against brain endothelial cells and neuronal nuclear proteins have been reported.

**Diagnostic criteria:**

- Abnormal EEG with epileptiform activity
- Aphasia (language & communication); children are unable to respond to their name and have difficulty understanding environmental sounds, such as a door bell.
- Autistic-like behaviors (avoidance of human contact, extreme pickiness over food, sleep disturbances, insensitivity to pain, and bizarre, inappropriate repetitive play)
- Behavioral problems (hyperactivity, aggressiveness, decreased attention, easily distracted, temper tantrums, and social withdrawal)
- Expressive language difficulties (the ability to speak is often seriously affected; some children lose their speech completely)
- Loss of bladder and bowel control
- Seizures (generalized or complex partial seizures in sleep)
- Visual disturbances (difficulty recognizing family and friends or common objects)
- Positive antibodies (IgG anti-brain autoantibodies) 45-50% individuals.

(Treatment of LKS is explained later with all epilepsy syndromes)

**Lennox-Gastaut syndrome:** Lennox-Gastaut syndrome is complex autoimmune epilepsy which is seen during 2 to 8 years of age. Lennox-Gastaut syndrome is one of the most severe forms of epilepsy. It accounts for up to 10 percent of all cases of childhood epilepsy, with slightly more males than females affected. It usually develops in children between 1 and 8 years of age, with 3 years being the average age of onset in Lennox-Gastaut syndrome.

**Types of seizures seen in LGS**

- **Tonic:** These attacks consist of stiffening of the body, with the eyes rolling upwards, dilation of the pupils and shallow, irregular breathing.
- **Atonic** or "drop attacks": brief loss of muscle tone and consciousness, causing abrupt falls.
- **Myoclonic:** consist of sudden arm or leg movement.
- **Atypical absence:** staring spells with some jerking and eye movements.

(Treatment of LGS is explained later with all epilepsy syndromes)



**West Syndrome (WS):** West Syndrome starts in the first year of life. The seizure of WS is a sudden bending forward and stiffening of the body, arms, and legs. Spasms tend to begin soon after arousal from sleep. Sometimes only the head and eyes are involved. Individual spasms typically last for 1 to 5 seconds and occur in clusters, ranging from 2 to 50 spasms at a time. Infants may have many clusters and several spasms per day. After five years of age these spasms are often replaced by other seizure types. West Syndrome is characterized by:

- **Infantile spasms**, (“Salam attacks”, because it's as if the baby is bowing down for a greeting)
- Brief head drop
- **Hypsarrhythmia** (disorganized, chaotic brain wave patterns, seen in EEG),
- Mental retardation.

(Treatment of WS is explained later with all epilepsy syndromes)

**Absence Epilepsy:** Usually seen in children this condition starts with episodes of staring which can last up to twenty seconds or more. There is associated blinking and the person does not respond during the attack to other people. Absence epilepsy has been seen in autoimmune diseases and in some cases only responded to treatment with steroids. It can be associated with Vasculitis such as Moyamoya disease.

Absence Syndrome is characterized by 3 per second spike and wave attacks seen on EEG.

**Epilepsia Partialis Continua (EPC):** This can be seen in a variety of conditions including infections, tumors or strokes, EPC can present like any seizure from just a finger jerking, to hand and arm movements spreading to the whole body rarely. The seizures can last a long time up to days. They are associated with GAD antibodies and respond to steroids, IVIg and plasmapheresis.

**Rasmussen's Encephalitis (RE) & Parry-Romberg syndrome (PRS):**

Rasmussen's syndrome is a chronic inflammation of the brain with recurrent seizures, it is a rare neurological autoimmune disorder, in which inflammation can spread to the whole affected side of the brain. There can be some atrophy of brain and extremities PRS presents with unilateral facial atrophy, seizures and sometimes vasculitis causing aneurysms.

**Symptoms of RE:** The disease starts slowly with weakness of the arm or leg giving the appearance of a stroke. The weakness will get worse with time and at the same time seizures start. These children may develop difficulty with talking. Usually it appears they have a stroke, as the baby stops using one hand, older children can have memory problems. Atrophy of the face in PRS is seen.

**Diagnosis of RE:** Magnetic resonance imaging (MRI) shows unilateral cerebral atrophy and foci of increased signal intensity in cortical grey and subcortical white matter. Multiple white matter lesions seen on the MRI scan can disappear with treatment. EEG will show seizure activity and slowing on the affected side. Antibodies against glutamate receptor are seen in Rasmussen disease. Individuals with PRS may have calcifications in the brain.

**Treatment of RE:** Recently it has been shown that if IVIg is given early, it stops the progression of the disease, seizures are controlled, and a complete reversal of the disease process is seen. It takes a month to see a complete improvement. Other therapies have included antiepileptics, **steroids**, antiviral agents, alpha-interferon, and immunoglobulin. In the past surgical removal of the involved brain was the only long-term treatment.

**Causes of autoimmune epilepsy:** The causes of autoimmune epilepsy are injury, post-vaccination, infections (Lymes, Mycoplasma, enteroviral meningoencephalitis, Toxoplasma gondii, Herpes encephalitis, AIDS-toxoplasmosis, streptococci) and many autoimmune diseases like SLE. Autoimmune epilepsy is also seen in paraneoplastic disorders with anti-Hu antibodies. Individuals may have anti-GAD antibodies in blood and spinal fluid.

The commonest causes of epilepsy syndromes in infants are infection due to cytomegalovirus and toxoplasmosis during the prenatal stage and the purulent meningitis, tuberculous meningitis and herpetic encephalitis during the neonatal and postnatal periods. The evidence of epilepsies in meningo-encephalitis varies according to the organism. All individuals with LKS, WS, and LGS need to be tested for IgG antibodies against Toxoplasma gondii. Cats can be the source of infection in the kids. Infants who have been exposed to cats are likely to have toxoplasmosis. Valporic acid has an affect against Toxoplasma and is an antiepilepsy drug for such cases. Presence of IgG antibodies against Toxoplasma gondii infection should be taken into account as a possible cause of Landau-Kleffner syndrome. In immunocompetent hosts pyrimethamine plus sulfadiazine are used for treating Toxoplasma.

**Tests for autoimmune epilepsy:**

- Glutamic acid decarboxylase antibodies(GAD), Antiphospholipid antibodies and Antinuclear antibody positivity and anti-GluR3 (anti Glutamate) antibodies.
- The spinal fluid IgG level, protein level and cell count need to be checked along with GAD antibodies. Elevated spinal fluid protein and elevated cell count are an indication of autoimmune disease. The spinal fluid glucose remains normal.
- Serum IgG level, IgG-subclass levels and IgA levels need to be measured. If the IgA level is low it indicates celiac disease, a high IgA level will suggest Henoch-Scholein purpura. Low IgG and low IgG-subclasses will be due to immune

deficiency, Dilantin can cause low IgG-subclass levels. Higher IgG-subclass levels are seen in response to an infection. Check Magnesium and calcium levels.

- M.R.I. scan or C.T. scan is done to take pictures of the brain, to look for damage. EEG is done to record brain waves. The EEG can show seizure activity and is especially effective if T1 and T2 electrodes are used in front of the ears. This helps record deep brain waves not usually seen by surface electrodes.
- Urinary porphyrin levels to evaluate for Porphyrria.

**Treatment for all autoimmune Epilepsy syndromes:** The treatment for autoimmune epilepsy is multi pronged. First fix any vitamin deficiency, fix mineral and fluid deficiency, use the correct drug, use the least amount of drug and use anti-inflammatory medication. If seizures increase respond by increasing steroids rather than anti epilepsy medication. In porphyria individuals the only epileptic drug that can be used is gabapentin. The first three steps are only for infants.

- **Diagnostic EEG** is done, to determine whether individual's seizures; and EEG abnormalities, are related to pyridoxine deficiency. In this approach, administer **pyridoxal phosphate** (vitamin B-6), 50-100 mg IV during diagnostic EEG; if dramatic improvement is noted in EEG, then the individual is having pyridoxine-dependent seizures. (**Only done for children**)
- **Pyridoxal phosphate** recommended dose for all epilepsy individuals is 10 mg/kg intravenous, then 10 mg/kg/day in four divided doses. This dose can be repeated if the seizures do not stop.
- In individuals responding to above treatment, start a combination therapy consisting of high-dose **pyridoxal phosphate** (40-50 mg/kg/day) and low-dose synthetic **ACTH** (0.01 mg/kg/day) is prescribed Monotherapy with pyridoxal phosphate provided excellent seizure control. Measure weekly B-6 levels to adjust dose.
- **Diet:** Use (chicken, fish, beef, rice, vegetables, fruits, milk products, sugar, jams and fruit juices). Things to strictly avoid are Gluten containing foods like Wheat, Rye, Barley, Millets and Oats. No beer or alcoholic products should be allowed. Above diet should be tried for three months if there is a benefit it should be continued and then the person is tested for Celiac disease. (See the gastrointestinal section). Magnesium supplements are very effective in controlling seizures (**Magnesium** and **calcium** levels should be checked in all individuals with epilepsy. Magnesium supplements have an anti-inflammatory effect. Magnesium is used in pregnancy induced epilepsy. )
- **Fluids:** Every individual needs to be placed on 8 glasses of water a day. The first thing in the morning is a glass of water.
- **Steroids:** In an emergency use Solumedrol one gram can be infused over one hour. Then oral prednisone or ACTH can be used. After the prednisone is given a decline

in clinical seizures and reduction in anti-GAD antibodies can be seen. Individuals with Myoclonic epilepsy respond even faster to steroids. Higher doses of steroids can also aggravate seizures.

- **Oral corticosteroids** are used more often and usually need to be maintained for a long period of time to prevent relapses. The recommended dose of Prednisone is 1mg/kg/day for 12 weeks (for 6 weeks daily steroids are given and from 7 to 12 weeks prednisone is tapered.). Treatment is long term, in long term immunosuppression look at the list of all the drugs used in the CIDP section.
- **Antiepileptic drugs:** As initial therapy, **valproic acid** is often chosen as it has anti inflammatory properties. This should start at the same time as steroids. The dosage is 15 mg/kg/day can be adjusted to achieve drug levels between 50 mcg/ml to a 100 mcg/ml. Fifty percent of the individuals are controlled by **valproate (VPA)** alone, in the rest VPA and lamotrigine combination can be used. Cases that have absence epilepsy, VPA alone or in combination with ethosuximide can be used. Other available drugs can be used, topiramate and Felbatol. **If clinical seizures increase try reducing the medications**, most seizures stop after reduction of the epilepsy drugs. This reduction in dose is accompanied by reduced clinical seizures, is commonly seen when multiple drugs are being used. Inflammation and irritation of the brain is triggered by higher antiepilepsy drug levels. When starting a new epilepsy drug start with a low dose, a higher dose will irritate the brain. If the EEG shows epilepsy activity, do not increase the dose of anti epilepsy drug. Increased activity may be due to inflammation, for which you need steroids, melatonin or pyridoxal. **Valproate** reduces L. Carnitine levels, thus supplements should be given to those individuals who have low Carnitine levels.
- **Benzodiazepines:** In West syndrome and LGS, clonazepam is used to prevent the Myoclonic jerks. If the proper dose of steroids is used, then steroids can control the Myoclonic jerks. Clonazepam is a long acting drug we recommend that one should try replacing this with **Lorezepam** which has less side effects and a shorter half life. Lorezepam is generally used as a sub lingual tablet to help prevent the progression of a seizure. It acts within minutes.
- **Supplements** for children with uncontrolled seizures occurring at night: 3mg of **Melatonin** given at night provides significant improvement in control of seizures in those children in whom epilepsy is uncontrolled. It takes a month to see all the benefits. Dose can be increased to 6 mg. It also improves the sleep cycle. Once, it is withdrawn seizures will return. It helps the Myoclonic epilepsy the best, and makes a good combination with Valproate.
- **Immunotherapies for epilepsy:** The immunotherapies have efficacy above standard antiepileptic treatment in some groups of individuals. CNS damage can result from autoimmune mechanisms which can be avoided if immunomodulation treatments are provided in time.

- IVIg or steroids should be the first line treatment in all these syndromes described above. IVIg can be started at a dose of, 0.5 g/kg body weight per day for 4 consecutive days. Then 500mg/kg can be given every 2 weeks to 4 weeks, for 5-6 months. During that period low dose of steroid can be used. The use of IVIG has been associated with an initial dramatic response in some individuals. Some individuals had an immediate response to IVIG initially and relapsed before eventually achieving a long-term sustained remission. To avoid relapses steroids should be given with IVIg and maintained based upon clinical response for three to six months.
- Cyclophosphamide can also be used to control seizures. In a case report, of a 2-year-old girl, who developed sudden onset of right hemiplegia, followed by generalized seizures, chorea-type movements, and severe weakness. Intravenous cyclophosphamide pulse therapy resulted in a complete improvement of her clinical symptoms. At age of six, she had recovered from epilepsy. Autoimmune mechanisms involving the antiphospholipid syndrome were considered to be the pathogenesis of this case.”
- Surgical treatment is reserved for individuals who have not responded to multiple medical therapies, has been followed in selected cases by a marked improvement in language skills and behavior.

**Alzheimer's:** Alzheimer's disease (AD) is an age-related autoimmune disorder that presents with a progressive loss in memory and deterioration of cognitive functions. The brain of an individual with AD exhibits extracellular senile plaques of amyloid-beta-peptide, intracellular neurofibrillary tangles that consist of tau protein and a loss of basal forebrain cholinergic neurons that innervate the hippocampus. In Alzheimer's disease (AD) there is increasing evidence that neurotoxicity is mediated by CNS inflammatory processes. Central nervous system (CNS) inflammation may predate the development of senile plaques and neurofibrillary tangles in AD and may prove to be a more sensitive marker of prodromal AD. Epidemiological studies suggest a protective effect of NSAIDs against development of AD. Individuals with Alzheimer's have lower levels of anti-beta-amyloid antibodies. In a study, Yale university investigators treated eight individuals. Of the eight treated individuals, seven have completed six months of treatment. All the individuals treated with IVIg improved and the disease showed a reversal in them, similar results were reported in a second study with IVIg in Alzheimer's individuals done in Europe. Another study found an increased incidence of the infection *Chlamydia pneumoniae* in the brains of deceased Alzheimer's individuals. This made a team from McMaster University in Canada to treat 101 individuals either with doxycycline and rifampin, or dummy pills for three months. Those given antibiotics showed significantly less mental decline. The authors conclude that a **three-month course of 200mg doxycycline and 300mg rifampin** results in less worsening in cognitive with Alzheimer's disease. These result likely represents a halt in disease progression, there was significantly less worsening in cognitive function at six months in the antibiotic group than in the placebo group.

A recent study reported by researchers from the University of Manchester in British Medical Journal, showed a high number of small strokes happening in Alzheimers individuals just within an hour. This can strengthen the infectious relationship of alzheimers disease. We can conclude that the infecting agent *Chlamydia pneumoniae* by molecular mimicry is turning on the immune system to attack blood vessels. Recent studies show a role for circulating beta-amyloid peptide in small blood vessels of the brain causing white matter disease.

Homocysteine, another marker of inflammation has been found to be elevated in individuals with AD. These individuals were also deficient in vitamin B12. Aluminum has been reported to cause alzheimers like dementia, in a large number of cases which developed in Guam the problem was resolved after changes in the diet of the local people.

**Symptom:** Memory loss for recent events is the only symptom of Alzheimers. People have difficulty recalling recent events of two or three weeks ago. They can talk normally, walk without problems and have no behavior issues in early stages of the disease.

**Diagnosis:** There are no routine tests to confirm Alzheimers so it's a clinical diagnosis based upon symptoms. All tests done on individuals are usually reported normal except;

- **EEG.** In early disease EEG will show exaggerated photic driving responses. We reviewed more than 60 consecutive individuals at NIH with Alzheimers and every individual had this phenomena.
- **FDG PET** scan shows hypometabolism of the parietal and temporal lobes in Alzheimer's disease.
- **Homocysteine, Folic acid & B-12** levels need to be tested for deficiency.
- **Check IgG** levels and IgG-subclass levels. (to screen for immunodeficiency)
- **MRI** scan of the head, to look for cerebral atrophy in the brain, strokes.
- **Anti-Gliadin** antibodies to screen for Celiac disease.

#### **Different conditions which can cause memory problems.**

- Forgetfulness for recent events can also happen due to travel, fatigue, and stress or vitamin deficiency like thiamine (vitamin B1, B12, B6 and thiamine).
- If the individual presents with behavior disorder then they are likely to have Frontal Temporal Dementia.(Multiple family members have this once you hold their hands the individuals have difficulty letting go of the hand)
- Vascular Dementia which is caused by multiple strokes, individuals have hypertension, difficulty walking and weakness.(is a treatable condition)

**Treatment:** There has been no effective treatment for Alzheimers. However multiple small studies have shown that following treatments worked in few patients.

- Three-month course of 200mg Doxycycline & 300mg rifampin for Chlamydia.
- If homocysteine levels are elevated, take sublingual supplements of B6, B12 and Folic acid. In individuals with B-12 deficiency one needs to look for anti-h-pylori antibodies. For treatment of H.pylori please see the Gastritis chapter.
- Avoid aluminum in medicines (buffered aspirin has aluminum, antacid therapy contains aluminum and, TPN feeding contains aluminum)
- Curcumin directly inhibits the production of amyloid plaques, the sticky substances that causes Alzheimer's disease. Turmeric, in studies, seems to cut the number of amyloid plaques in half. A tablespoon of curry a day, or 200 mg of curcumin works in reducing the plaques.( Research study done at UCLA)
- Fish oil or aspirin taken daily to reduce inflammation and prevent recurrent small strokes, which were reported from a study done at University of Kentucky.
- Colostrum is rich in IgG. Colostrum in studies has been found helpful.
- Mild physical activity three times a week reduces the risk for alzheimers.
- Calories need to be restricted and the individual hydrated.
- If IgG levels are low the individuals has immunodeficiency then treat with IVIG.

Aspirin is used to reduce inflammation and strokes in Alzheimer's. This reduces the risk of developing Alzheimer's by 55%. The individuals had to be on aspirin at least two years before any symptoms of Alzheimer's appeared. Fasting is recommended at least one day a week to avoid Alzheimers. Use a high fat diet (high in Omega-3 and low in Omega-6) found in walnuts, almonds, cod liver oil or fish oil, whole wheat and canola oil.

**Neuromyelitis optica-Transverse Myelitis:** Transverse Myelitis is a inflammation of the spinal cord. Myelitis is sudden onset and is caused by autoimmune process. Cases may have a preceding history of flu, infection or vaccination such as hepatitis.

**Neuromyelitis Optica or Devics Disease:** These conditions have an association of Transverse Myelitis (TM) with optic nerve inflammation. The disease may have a relapsing, remitting course and responds to steroids, sometimes poorly. NMO has a poor prognosis, due to the occurrence of necrosis within lesions. Relapses are commonly treated with corticosteroids and people with recurrent attacks may be managed with chronic immune suppressive treatments. Intravenous gamma globulin (IVIG) and plasma exchange are reasonable treatment options because NMO is believed to be antibody mediated and associated with S.L.E. Case reports of Lymes with optic neuritis in both eyes have responded to **Doxycycline**. The dose is 200mg daily for a week then, 100 mg daily for a week.

**Transverse Myelitis (TM):** Myelitis means inflammation of the spinal cord; transverse refers to involvement across one level of the spinal cord. Myelopathy is a general term for a disorder affecting the spinal cord. Infectious agents have a protein which resembles or mimics the structure of myelin in the spinal cord. When the body mounts an immune

response to the invading virus, it also responds against the spinal cord myelin with which appears similar to the virus. This leads to inflammation and injury within the spinal cord. The nerve fibers in the spinal cord carry all the instructions from the brain to the extremities, they also carry back sensory information to the brain. Inflammation within the spinal cord interrupts these information links and causes the symptoms of TM which include limb paralysis, sensory disturbance, with bowel and bladder dysfunction

### **Triggers of Autoimmune Transverse Myelopathy or Myelitis & NMO:**

- **Systemic** lupus erythematosus, Sjogren's syndrome; Sarcoidosis, Multiple Sclerosis, Paraneoplastic syndrome and antiphospholipid syndrome.
- **Bacterial:** Mycoplasma pneumoniae, Lyme borreliosis, syphilis, tuberculosis, Rocky Mountain spotted fever
- **Viral:** herpes simplex, herpes zoster, cytomegalovirus, Epstein-Barr virus, enteroviruses (poliomyelitis, Coxsackie virus, echovirus), human T-cell, leukemia virus, human immunodeficiency virus, influenza, rabies
- **Post-vaccination :** TM has been reported within a few days or few weeks of the following vaccines.(rabies, cowpox, diphtheria-tetanus-pertussis, measles or rubella, Japanese B encephalitis)

Symptoms of Transverse Myelitis & NMO:

- Back pain or a band like sensation going around the abdomen is one of the earliest symptoms. Tight banding sensation around the abdomen
- Leg weakness or paralysis if the myelitis involves the lower spine.
- Inflammation at neck level causes numbness of the face and weakness in the arms.
- Bladder involvement is seen with loss of urinary control and bowel sphincter control may be affected.
- Vision problems & blindness are reported in Devic's disease.

**Tests:** MRI scan of the spine or the brain to look at any damage in those areas. Spinal tap is done to take a sample of the spinal fluid and check antibodies against appropriate bacteria suspected in the particular case. A vitamin B-12, B-6 and thiamine levels are done to check for deficiency. Antigliadin antibodies are done to check for Celiac disease. R.P.R is done to check for syphilis and testing for HIV can be obtained in suspected cases.

Antiphospholipid syndrome can present with optic atrophy and transverse myelitis with positive IgA type antiphospholipid antibodies.

### **Treatment of Myelitis & NMO:**

- Early treatment provides the best results. Combination treatment with steroids and IVIg is the most effective. High dose steroids or a combination of steroids and cyclophosphamide has been effective. Some individuals appear to become glucocorticoid dependent and experience relapses when the dosage of prednisone is



lowered. Plasma exchange (PE) may be tried in individuals who do not respond to glucocorticoids. NMO treated with PE showed moderate or marked improvement.

- Those with exposure to mycoplasma infections get Doxycycline 200mg once a day for two weeks. Prednisone and Doxycycline is a good initial treatment.
- IVIg is effective in all cases of TM at a dose of 500mg/kg for 4 days.
- In individuals with positive antiphospholipid lipid antibodies simply start anticoagulation with heparin, coumadine and high dose of steroids.
- Replace vitamins if any deficiency is found.

### **Chronic inflammatory Demyelinating Polyradiculoneuropathy or (CIDP)**

The nerves in our body have an outer covering which is like a roll of toiled paper wrapped around the axon (axon is the filament carrying nerve impulse from the neuron). The myelin helps conduct electricity in our body by a process called salutatory conduction (current jumps from one myelin cell to the other). The peripheral nerves carry information from the spinal cord to the muscles. Due to myelin nerve impulse are transmitted very fast in our body. In GBS, CIDP and autoimmune neuropathy the myelin is attacked and damaged, resulting in numbness and weakness, burning type pain. If the attack against myelin can be turned off, then Schwann cell in the nerves will develop more myelin and the person feels back to normal.

CIDP represents about one third of all initially undiagnosed neuropathies (nerve disease). Repeated attacks of weakness or numbness are common. A relapsing course with partial or complete recovery between recurrences is seen. The periods of worsening and improvement usually last a month or many years. Younger individuals are said to have a higher frequency of relapsing course as disease improves and worsens again. Relapses can happen after 7-8 years. Individuals with CIDP respond to immunosuppressive therapy. CIDP usually occurs within a few weeks after an infectious event. Both respiratory and gastrointestinal infections have been implicated as a cause. CIDP can also be slowly progressive and develop along with diabetic neuropathy. Most cases are usually misdiagnosed as polyneuropathy and told nothing can be done for them. Without anti-inflammatory treatment many will develop autoimmune heart disease, skin lesions, inflammation of the blood vessels, thus early intervention is recommended.

**Symptoms of CIDP:** People with CIDP have repeated attacks of weakness that last for a month or more. Sensory complaints consist of numbness and tingling in hands or feet. Burning type sensation and pain will force the individuals to seek medical attention. The peak incidence is 40-60 years of age. This neuropathy is seen in diabetics, and is slowly progressive. The disease may start as back pain going down the legs or a sudden hand weakness. Autonomic dysfunction termed dysautonomia (dysfunction of the autonomic nervous system) can occur. Symptoms of dysautonomia consist of irregular cardiac rhythm, diarrhea, constipation, dizziness on standing up, burning type feeling, feeling of swelling. Increased sweating which could be on one side of the body. Discoloration of skin below the

knees may be seen. Loss of consciousness while the person is standing can happen, this type of CIDP is called autonomic small-fiber neuropathy and is discussed with the seven variants or subtypes of CIDP.

**Neurologic exam** in general shows neck flexor weakness distinguishes CIDP from other neuropathies. Facial muscles may be weak. Eye movements can be affected in CIDP causing double vision. Deep tendon reflexes are absent or depressed and rarely increased. Sensory findings are mild and often include impaired touch and vibratory sensation, with less involvement of small-fiber sensation (pain and temperature). It is common to see bilateral or unilateral weakness of shoulders, hips, hands and feet in most individuals.

**CIDP Variants -1: Lewis-Sumner syndrome:** (LSS) causes numbness and weakness of the hands or hips. The difference between LSS and Multifocal Motor Neuropathy is that no sensory involvement is seen in MMN, with a lack of anti-GM1 antibodies in LSS. It is also called **multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)**.

There have been case reports with a normal EMG/NCV in LSS. However with magnetic stimulation the individuals were found to have proximal conduction blocks in the arms.

**Symptoms LSS: 1)** LSS presents frequently with arm involvement, mainly involving the wrists and hands, causing syndromes resembling either the little or ring finger becomes numb and weak or the thumb middle and index fingers are weak and numb. It can involve the whole hand. are seen. Individuals have difficulty opening and closing their hands. They have difficulty driving a car, opening a door or holding a spoon. Cannot flex or extend the fingers due to weakness.

**LSS: 2)** LSS can also present with sudden onset of hip weakness. Individuals note difficulty in getting out of a chair, difficulty climbing stairs and weakness in the thigh. On examination the individual cannot elevate the affected knee while sitting (Quadriceps weakness). Mild wasting, and fasciculations, with some sensory involvement is seen. This can be misdiagnosed as femoral neuropathy or Lumbar plexopathy. **Case report:** In a person with hepatitis-C virus (HCV) infection developed (LSS). The neuropathy worsened after IVIg, remitted after intravenous methylprednisolone, relapsed during interferon-alpha, but responded again to steroids continued for 70 weeks with clinical remission and without worsening of hepatitis.

**Test for LSS: EMG/NCV** multiple motor conduction blocks are seen, predominantly located in the forearm, whereas demyelinating features outside the blocked nerves are rare. Abnormal distal sensory potentials are found in majority of the individuals. Rarely the conduction block can be up in the arm and EMG/NCV may look normal.

**Treatment: LSS** responds well to IVIg or steroids.

**CIDP Variants-2: Multifocal Motor Neuropathy:** MMF is purely a motor or weakness issue. No sensory nerves involvement is seen. It affects men much more than women. Some individuals complain of numbness, about 50% individuals have IgM antibodies to

ganglioside GM1. Diagnosis depends on the demonstration of short focal areas of partial motor conduction block caused by demyelination at sites not vulnerable to entrapment. Sensory conduction is normal across the same segments. Even if no definite conduction block is found in an otherwise typical case, a trial of treatment may be indicated.

**Symptoms / examination MMF:** A progressive muscle disorder with muscle weakness in the hands, there is asymmetric involvement of the muscles. Muscle wasting, cramping, and twitching of the muscles are seen. The disorder is sometimes mistaken for amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). Tendon reflexes are often absent or weak. The weakness can spread to involve the legs and feet causing individuals to be confined to wheelchairs. In some individuals the tendon reflex can be increased.

**Tests for MMF:** Antibodies against GM1 ganglioside are present a lipid present on nerve fibers. These antibodies are rarely present in any other disease. The EMG/NCV characteristic finding is, **conduction block**. Nerve conduction studies show blockade of impulses at focal sites along the course of motor axons (motor conduction block) providing evidence that the site of disease lay in the peripheral nerve. The phenomenon of conduction block had been described in individuals with sensory-motor neuropathies (chronic inflammatory demyelinating polyneuropathy (CIDP)). Conduction block is thought to result from focal regions of immune-mediated demyelination along the course of the nerve.

**Treatment:** MMF responds to IVIg.

#### **CIDP Variants-3: ANTI-MAG (Myelin Associated Glycoprotein) Neuropathy:**

Individuals with MAG polyneuropathy who have antibodies to myelin-associated glycoprotein (MAG) has a slower, progressive course, this condition causes weakness and numbness of the legs, predominantly distal slowing of motor conduction, and poorer response to therapy.

**CIDP Variants-4: MGUS Monoclonal gammopathy of unknown significance, MGUS (or benign monoclonal gammopathy, BMG):** Monoclonal gammopathy of unknown significance, MGUS is a part of CIDP. Any neuropathy seen in MGUS is to be considered and treated as CIDP. MGUS usually has (IgA or IgG or IgM) immunoglobulins elevated in the serum. The neuropathy is mainly seen in males. It is a combined sensory/motor neuropathy involving the lower extremities and sparing the cranial nerves. In women this advances rapidly from feet to hands and then involves the face. It can cause severe pain. Higher incidence of Myeloma can be seen in these individuals. The **POEMS** syndrome of polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes is occasionally seen in some cases.

**CIDP Variants-5:** Another rare paraproteinaemic neuropathy is (**CANOMAD**) Chronic ataxic neuropathy with ophthalmoplegia (loss of eye movements), IgM-paraprotein, cold agglutinins (antibodies respond to cold temperatures), and disialoganglioside-antibodies.

**Symptoms of MGUS:** Individuals present with a lot of pain and burning, to reduce the pain they keep their hands and arms on ice. Pain is severe at night. Case report: 70-year-old man presented with double vision, new onset of relapsing neuropathy, elevated sedimentation rate, IgM monoclonal paraprotein, cold agglutinins, and antidisialosyl IgM antibodies, features of the acronym CANOMAD (chronic **a**taxic **n**europathy with **o**phthalmoplegia, **M** protein, **a**gglutination, and **d**isialosyl antibodies). The individual also had renal failure associated with this syndrome. Treatment with corticosteroids improved both the neuropathy and renal failure.

**Treatment of MGUS:** Is like CIDP with steroids, plasmapheresis and IVIg.

**CIDP Variants-6: Small Fiber Neuropathy:** Small fiber sensory neuropathy (SFSN) is a disorder in which only the small sensory superficial nerves of the skin are affected.

Individuals experience sensory disturbances that start in the feet and progress upwards.

Some individuals with SFSN experience quick onset burning pain and numbness over the whole body, including the body and even the face. These individuals can have autoimmune diseases, celiac disease, amyloidosis, erythromelalgia or diabetic neuropathy. Nutritional and toxic causes include excessive use of alcohol, amidrone, arsenic, bornic-acid, cyanide and hexacarbons (glue sniffing). Inherited causes include, hereditary sensory neuropathy Type I (HSN1) which causes high arched feet with hammer toes.

The symptoms of small fiber sensory neuropathy are primarily sensory in nature and include unusual sensations such as pins-and-needles, symptoms of burning sensation affecting the feet, pricks, tingling and numbness. Some individuals may experience pain or coldness and electric shock-like brief painful sensations. Since SFSN usually does not involve large sensory fibers that convey balance information to the brain or the motor nerve fibers that control muscles, these individuals do not have balance problems or muscle weakness. In most individuals, these symptoms start in the feet and progress upwards. In advanced cases, it may involve the hands. They can also develop dysautonomia, with erectile dysfunction, diarrhea or constipation.

**Test:** EMG/NCV will be normal in small fiber neuropathy. **Skin biopsy** looking at nerve fibers is abnormal. The quantitative sudomotor axon reflex test (QSART) is used to assess the small nerve fibers, which are linked to the sweat glands. Nerve biopsy is usually reported as normal.

**Treatment** is similar to CIDP guidelines. All the individuals need to be evaluated for celiac disease. All should be trying a aspirin a day unless contraindicated.

**CIDP Variants-7: Distal acquired demyelinating sensory neuropathy.** This can present is children as an ataxia (walking like a drunk). Individuals mainly have a balance problem, there can be sensory involvement.

**Symptoms / examination:** Individuals have unsteady and clumsy way of walking, and pins and needle feeling in their hands or feet, they have frequent falls. On examination they have reduces vibration and joint position sense, loss of pin prick sensation in the feet or

hands. Reflexes are intact.

**Test:** EMG/NCV can be normal or may show slight slowing of sensory nerves.

**Treatment** is with IVIg or steroids.

**Associated medical Conditions with CIDP:** CIDP can be seen together with Multiple Sclerosis. Many such cases have been reported showing (White spots on the MRI combined with a neuropathy). Celiac Disease will also show a similar involvement of white spots in the brain with a neuropathy. Similar involvement of brain and nerves is also seen in Lupus, Inflammatory bowel disease like ulcerative colitis and Crohn's. In the Bowel diseases h-pylori is the main pathogen and antibodies against h-pylori should be tested and H-pylori eradicated with the antibiotics protocol described in the stomach chapter. Individuals with diabetes, SLE, Sjogrens, who have a progressive neuropathy it's more likely to be CIDP superimposed on their diabetic disorder. It is better to assume that a new neuropathy developing in individuals with arthritis, heart disease and lupus is likely to be CIDP.

**Diagnosis: CIDP: CIDP: Diagnostic Criteria ALERT** American Association of Neurology (AAN): Criteria are only for Research Studies. This should not be used in clinical diagnosis. AAN Electrophysiologic criteria: Require 3 demyelinating range abnormalities (slow conduction velocity, prolonged distal motor latencies or F wave latencies or conduction block) in 2 nerves. These criteria should not be used in Clinical Practice as more than 50% of the individuals will not be diagnosed by this criterion. Majority of individuals seen in clinical practice fail to meet all of the above criteria.

**Laboratory Studies: CSF Protein level** is increased significantly in 80% of individuals usually between 50 and 200 mg/Dl. Usually normal in small fiber CIDP.

**EMG/NCV** test shows findings of a slow nerve conduction (demyelinating pattern) or slightly slow (Axonal pattern) neuropathy are usually seen. There are prolonged distal latencies (the time difference measured after shocking a nerve over a segment). Absent or prolonged F-wave latencies, as the disease progresses, individuals tend to develop secondary axonal degeneration. **Individuals can have a normal EMG/NCV in small fiber CIDP.** The types of nerve cells that are damaged in painful sensory neuropathies (small, unmyelinated and thinly myelinated axons) are not well studied by EMG and NCS, and these tests can give false "normal" results in individuals with small-fiber neuropathies.

**Peripheral nerve biopsy (A skin biopsy should be considered in place of a Sural nerve biopsy)** In the past, the best way of getting information about sensory neuropathies that cause pain was surgical removal of a part of the sural nerve at the ankle. This left individuals with permanent numbness, and caused other complications in some individuals. Skin biopsy, a minor procedure with no serious complications, gives much of the same information. In addition, skin biopsy may even be more sensitive than sural nerve biopsy because it samples the nerves closer to their endings in the skin, where disease starts. Nearly all parts of the body have microscopic nerves running through them to allow

sensation and movement. Skin biopsies can be processed in a way that allows us to see and count the number of sensory nerve endings, and to look for any neural abnormalities. Even in Leprosy skin biopsy is equally good when compared with the sural nerve biopsy. Current clinical standards to diagnose CIDP do not recommend a nerve biopsy. As the skip lesions of CIDP may or may not be seen in sural nerve biopsy. After biopsy the individual usually has a permanent sensory deficit, the sensory loss in the foot accompanied by pain, is worse than the original disease. We have seen individuals who are worse off due to biopsy. Finding of inflammation on the nerve biopsy, although rare, definitely confirms the diagnosis. Findings of predominant demyelination on the nerve biopsy can be used to confirm the clinical presentation and suggest a diagnosis of CIDP. However, the absence of inflammation does not entirely rule it out. The best technique for a sural nerve biopsy is described by an Austrian team. Where they only remove a 10mm piece of the sural nerve and reattach the stumps by microsurgical repair. They claim none of their individuals have any complaints of pain or sensory loss.

**Recommended blood tests for neuropathy evaluation:** Vitamin levels should be tested in all individuals **Cynocobalamine (B12), Pyridoxine (B6), Thiamine**, Niacin, Alpha tocopherol (E), Folic acid, are recommended tests. Thiamine deficiency, in particular, is common among people with alcoholism because they often also have poor dietary habits. Thiamine deficiency can cause a painful neuropathy of the extremities.

- **Thyroid function test** (TSH & T4, anti thyroid antibody)
- **Vasculitis evaluation** (CRP or E.S.R.) (ANA and antiphospholipid antibody).
- **Oral glucose tolerance** test or hemoglobin A1C
- Antibodies (anti-MAG, anti-GM1, anti-Sulfatide, anti-GALOP, Anti-GQ1b)
- **Antibodies celiac disease** (Anti gliadin antibody)
- **Lyme disease**, (Borrelia burgdorferi antibodies)
- AIDS testing (HIV antibody test)
- **Syphilis**, (RPR test)
- Hepatitis C (Anti-HCV (antibody to HCV)
- Heavy metals screen for (arsenic, lead, mercury, and thallium).
- Anti-Hu antibody (antibody for a pure sensory neuropathy underlying malignancy)
- SPEP Serum protein Electrophoresis (For Myeloma)
- IgA level, IgG level, IgG-subclass levels (to evaluate for immunodeficiency)
- Antiphospholipid antibodies in CSF (will need heparin, aspirin or coumadine)
- Serum Homocysteine levels ( B-12 levels are unreliable, homocysteine is a better marker for B-12, B-6 deficiency and suggests inflammation)
- **Sarcoid** cases have more pain than sensory loss and responds to steroids. Accompanied by joint pains, weight loss and fatigue. Angiotensin-converting enzyme level is elevated and chest X-ray is abnormal.

- **Porphyria** needs to be checked in people with autonomic neuropathy and weakness, may have abdominal pains, porphyrinogens in blood and urine are elevated. Urine left in a cup becomes dark on sunlight exposure and during attacks. Cerebrospinal fluid abnormalities show elevated protein. However, accompanying psychological features, a shoulder or hip asymmetric weakness suggests porphyria.
- **Amyloid** neuropathy typically affects pain & temperature fibers, but occasionally individuals can develop large-fiber neuropathy as well. Carpal tunnel syndrome or painful peripheral neuropathy, sensory or mixed neuropathy is also seen. Initial symptoms of sexual impotence, cardiac problems and low blood pressure on standing develop. Urinary proteins are elevated.

**The protocol for CIDP treatment:** James Austin first documented the steroid responsiveness of Chronic Inflammatory Demyelinating Poly neuropathy in 1958. Prednisone was used orally, the trend is changing towards intravenous pulse doses. The mean time for initial response is two months. After attaining maximum benefit (usually 6-12 months), prednisone is slowly tapered. Unfortunately, the tapering of prednisone may result in a relapse of CIDP.

More recent studies show that IVIG, prednisone and plasma exchange are all beneficial. Plasma exchange performed twice weekly for 3 weeks generally resulted in transient improvement in progressive and recurrent cases. Intravenous immune globulin (IVIG) has been found to be beneficial and is considered the best first treatment.

**Infections: (Try to get rid of any associated infection in autoimmune cases)** Since autoimmune diseases in general and GBS & CIDP in particular are clinical presentations of many different types of infectious diseases, some of the known etiologies are Borelli, Campylobacter Jejuni, Brucella, Chlamydia pneumonia, Coxiella burnetii, Mycoplasma pneumoniae, Legionella pneumophila, Listeria monocytogenes, H.I.V and Treponema pallidum. Many individuals who were treated with antibiotics not only got better but had no further attacks. The antibiotics commonly used have been **Doxycycline**, Zithromax, Biaxin, Ceftriaxone and Penicillin.

- In cases of GBS induced by Coxiella Burnetii, 14 days doxycycline treatment (200 mg daily) induced rapid and complete recovery. Prolonged antibiotic treatment may be required to prevent relapsing infection from the resistant bacterium. In chlamydia pneumonia treatment with Zithromax, Biaxin, Erythromycin or Ciprofloxacin.
- Cases of GBS where Lyme disease is the cause, are treated with Ceftriaxone intravenous for two weeks or Doxycycline 200mg for two weeks orally.
- People in areas of West Nile Virus (WNV) need to be alert for GBS, CIDP caused by WNV and these cases should be promptly treated by Doxycycline.
- Cases acquired by Mold the use of IVIg with itraconazole results in resolution.

- CIDP/ GBS associated with hepatitis-C virus infection is treated by interferon-alpha-2b and ribavirin. Viral eradication is confirmed during the 4th week of treatment and is followed 3 weeks later by neurologic improvement. The individuals have resumed normal activity within a year of this treatment.
- Cytomegalovirus infection use ganciclovir (5 mg/kg BID) for 4 weeks.
- Treatment with antibiotics in the first couple of days of campylobacteriosis is recommended for those with weakened immune systems, pregnant women and people with relatively severe symptoms. The use of antibiotics called fluoroquinolones to treat disease in chickens is creating strains of drug-resistant campylobacter in humans.
- Finding a source of inflammation in a individual with CIDP and then removing it also benefits the individuals, after adenotonsillectomy, the individual's CIDP has gone into remission.
- HIV virus and aids can present with neuropathy responds to IVIg.

Finally toxins like botulinum (Botox) have been linked to development of CIDP if diagnosed early can be completely treated with IVIg. Individuals getting Botox injections should be alert to any new symptoms of weakness and numbness.

**Diet:** Celiac disease can present as CIDP it needs to be ruled out. However some individuals may still have the Celiac disease and this does not show up on their blood tests we recommend that individuals try the Gluten free diet to see if they improve. Please read the diet section for guidelines.

#### **Immunomodulatory treatment for autoimmune diseases including CIDP/GBS.**

Immunomodulatory treatment is started after making sure that any infection present in the body has been cleared up. Vitamin, mineral and amino acid deficiency should be addressed. The individual should be on dietary recommendations provided in the diet section. Those individuals with positive antiphospholipid antibodies should be on either aspirin or subcutaneous heparin, usually these are elderly men with a sensory-motor neuropathy, they are at high risk of having strokes.

#### **There are three short term treatments:**

- **1-IVIg:** is the first line treatment in USA it has reached this position due to ease of infusion in the individual's home. IVIG is the only treatment recommended during pregnancy. It is an expensive treatment and needs to be repeated monthly. The earlier it is given in the course of CIDP the better the response. The starting dose is 500mg/kg given on consecutive or alternate days for a four day course. The rate of infusion is controlled to around a 100-200 cc per hour. Usually a 5% solution is recommended. We have used one aspirin daily to prevent thrombosis and oral water



hydration to overcome any renal problems. This dose of IVIg is repeated usually up to five months. In the meantime the individual is started on an immunosuppressant. This immunosuppressant is started with the intention that it will become the primary pharmaceutical agent in the long run. The immunosuppressants are listed under **(List A) below**. IVIG will lose its efficacy in the long run and it has to be replaced. If the IVIg does not work then it is recommended to use one gram of intravenous steroids with IVIG. Combined treatment with steroids is recommended in most cases. For the long run IVIg should only be used in those individuals who have exhausted the agents in **(List A)**.

- **2a-Steroids:** Some individuals only respond to steroids. For long term use it is recommended to use alternate day steroids or intravenous steroid pulses. Intravenous route 1 gram of Solumedrol is given over an hour. Then the individual can be maintained on a oral dose. Starting with 1mg/kg/day after 1 to 2 weeks the dose can be tapered to adjust to clinical response. Once the dose is being tapered a long term immunosuppressant should be started choose from Imuran, cytoxan, Methotrexate, cyclosporin or any of the agents listed under list A.
- **2b-Steroid Pulses:** Initial dose of 1000 mg/daily of intravenous-methylprednisolone (IVMP) on every fifth consecutive day, followed by 1000 mg IVMP every-week for the next month. IVMP is then reduced in frequency and dose over a period of 2 months continuing to 2 years. Individuals are maintained with long-term high-dose intermittent IVMP every 2 to 12 weeks for up to 10 years with stable strength. In a few individuals, the intermittent high-dose IVMP is changed to intermittent oral corticosteroid if poor veins limit IV line access or difficulty getting to an IV infusion center. Rare adverse effects occurred in only 1 or 2 individuals receiving IVMP or oral prednisone, included cataracts, insomnia, pneumonia, ruptured diverticulitis, herpes- zoster, mood changes, and cramps. Lower doses are better tolerated by some individuals. High dose of steroids beyond 6 months are not advised and switching to lower doses combined with a second drug from the list below is recommended. Aspirin treatment should be given to all individuals on long term steroids to prevent avascular necrosis of bone. (avascular necrosis is a vasculitis in the bone)
- **3-Plasmapheresis:** Helps remove abnormal antibodies circulating in the serum. This procedure is only done in hospitals. During the procedure individuals blood is run through a tube to the plasmapheresis unit, which spins the blood at high speeds. During the spinning plasma and antibodies are removed. Fresh plasma or fluids are added to the individuals blood cells and returned back to the individual by a intravenous line. Usually 3 plasma exchanges per week are done for first 2 weeks. If the procedure is available it should be tried on those individuals who have not responded to IVIg and steroids. Low blood pressure, allergies to equipment, low potassium and low serum calcium can occur during the procedure.

**List A:** Agents used for **refractory individuals in autoimmune diseases**. Some of the successful immunosuppressive treatments reported are,

- **Cyclosporine A (CyA)** The daily dose of CyA should be 3 mg/kg/day. If individuals respond to cyclosporine, remission can be maintained for 2 years, after which the dose can be slowly reduced over 1 year. Eventual withdrawal should be considered. In a recent trial all fourteen individuals with CIDP on cyclosporin improved.
- **Methotrexate** can have a relatively rapid onset of benefit within (months). It can be useful when corticosteroids or Cyclosporine-A are ineffective or contraindicated. With routine monitoring, serious side effects are uncommon. Methotrexate dose is started at 2.5 mg once a week, increased to **7.5** to 25 mg orally. Taken once a week on weekends. CBC and liver functions need to be monitored. The drug can cause serious liver disease in presence of alcohol.
- **Azathioprine (Imuran)** is a broad spectrum immunosuppressive agent and may have a steroid sparing action, provides long-term immunosuppression with relatively few side effects the dose is 2.5 to 3 mg/kg daily. It may be useful to reduce needed doses of corticosteroids. However, it can take two to six months to show benefit and some individuals do not improve at all. It works well in individuals who have chemical exposures which triggered CIDP. Azathioprine is metabolised by enzyme and 10% of the population may have a deficiency. Measurement of enzyme values identifies the heterozygotes (different genes), whose dose should be halved, and homozygotes (similar genes), who should probably not be given the drug. It should not be used with allopurinol.
- **Cyclophosphamide** is an alkylating agent, which predominantly depletes B lymphocytes 2.0 to 2.5 mg/kg/day, given as a single dose each morning. (CIDP) Individuals who were refractory to conventional treatment have responded to this treatment with high-dose. Individuals should not get pregnant on this treatment.
- **Etanercept**, 25 mg twice per week. Some CIDP individuals may have significant improvement on this treatment. Etanercept is an injectable drug that blocks tumor necrosis factor alpha (TNF alpha) and is used for treating rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.
- **Interferon A:** Interferon beta-1a (Avonex) down regulates inflammatory responses has shown benefit in refractory CIDP individuals received at a dose of 30 microg once weekly for 6 months is used.
- **Mycophenolate mofetil (MMF)** Cellcept mean dose, 2 g/day given for an average of 14 months). MMF showed a good response in 1/3 of the individuals treated.
- **Rituximab** is an intravenous drug that is used to treat B-cell non-Hodgkin's lymphoma. It belongs to a class of drugs called monoclonal antibodies. Monoclonal antibody against CD20 antigen on B-cells. It represents a successful therapy in

otherwise refractory autoimmune diseases and CIDP. Initial: 375 mg/M2 intravenous, I/V Twice Weekly Maintenance: 375 mg/M2 IV every 10 weeks. TB Should be ruled out before starting treatment with rituximab. If a individual has failed treatment with steroids, IVIg, cyclosporin, plasmapheresis, Rituximab will be effective with just 4 weeks of treatment.

- **Hyperbaric Oxygen Therapy works for polyneuropathy and autoimmune diseases caused by infections.** The theory states that more oxygen enters the body under higher pressure and improves healing. Increased oxygen also helps eliminate infective organisms like Mycoplasma and Borrelia from the body.
- **Magnesium** supplements can help reduce inflammation and relive pain. Dose is 400 mg twice or three times a day. In diabetic polyneuropathy Magnesium supplements used for a year have led to an improvement of nerve function significantly. Vitamin D and calcium supplements are also effective in some cases.
- Bovine Colostrum has been used to reduce muscle stiffness, with good results. The dose needs to start at 400-500 mg twice a day and go to 1-2 grams a day as needed.
- Stem-cell-transplant has been used in CIDP and autoimmune diseases with success, in the future this treatment will become as simple as giving a injection.
- **DHEA** is a hormone replacement health supplement which builds muscles and improves strength. It also improves osteoporosis.
- **Sex:** Autoimmune individuals may see reduced sexual function, especially men. It is recommended they use a half an inch wide rubber band around the penis shaft. This will improve erectile function. Women need to use lubricants due to vaginal dryness.

**Prognosis of neuropathy and autoimmune diseases:** Unlike the overall good prognosis in Guillain-Barré syndrome, Chronic Inflammatory Demyelinating Poly neuropathy is less likely to have spontaneous remissions and is often associated with prolonged neurological disability. Although 95% of individuals will show initial improvement following immunosuppressive therapy, the relapse rate is high. If left untreated then individual can become severely disabled. Those individuals not responding to above treatments should be checked for a source of infection and to see if they have some other cause of neuropathy such as Celiac Disease. Please read the discussion on celiac disease in the Gastro Intestinal Disorders Chapter. With treatment most individuals do well with autoimmune disorders. Any disorder with Giant cell involvement has a aggressive course and delayed treatment shows higher mortality and organ damage.

**CIDP in Children:** Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is rare in children. Children demonstrate many similarities to adults. Antecedent events such as a preceding flu, illness or vaccination are seen in fifty percent of the children. The onset of symptoms was usually quick.

**Symptoms:** Children frequently present with weakness and loss of reflexes accompanied by sensory loss. Pain in the back and cranial nerve involvement is rare. Cerebrospinal fluid protein levels are usually elevated. They usually present with difficulty in walking, tripping, difficulty going upstairs and rarely just one leg may be involved. Request a neurology appointment a primary care doctor may not be able to diagnose this. (Suggest the diagnosis Guillian Barre Syndrome).

**Testing:** On electrodiagnostic testing, children may show a normal or slightly abnormal nerve study thus ENG/NCV. Nerve Biopsy is unreliable in children with CIDP and not a recommended study. Repeated EMG/NCV testing is not recommended as slowing of nerve conduction can persist for long periods after clinical recovery. Spinal tap can show increased protein. Antibodies for H.pylori, Borrelia need to be checked.

**Treatment:**

- Tonsils and Adenoid glands need to be checked for inflammation and treated. Lymes disease should be checked. (Full description is under CIDP treatment section). The initial response of children with CIDP to immunomodulating therapy is excellent. Intravenous high dose Steroids are contraindicated in children and have been shown to make their condition worse. I.V.I.g and cyclosporine combination has been very effective.
- In resistant chronic inflammatory demyelinating neuropathy, in addition to prednisolone and immunoglobulin, plasma exchange, azathioprine, cyclosporine, methotrexate, and cyclophosphamide can be tried at different times in different individuals. Childhood chronic inflammatory demyelinating neuropathy responds to conventional treatment and generally has a favorable long-term outcome.
- I.V.I.g given at a dose of 500mg/kg for 4 days then 500mg/kg every two weeks for two months and then 400mg/kg every four weeks for 4 months. Several studies have indicated clinical improvement after treatment with prednisolone, plasmapheresis and intravenous immunoglobulin. M.R.I. study of the lumbar nerves, can show enlargement, which will respond to prednisone treatment.

**Guillain-Barre Syndrome:** (GBS) Guillain-Barre syndrome, the most frequent cause of acute neuromuscular paralysis, occurs 1-2 wk after various infections, vaccination in particular, and Campylobacter jejuni enteritis. Molecular mimicry between the bacterial and human Myelin is seen as having relationship to the autoimmune cause of Guillain-Barre syndrome.

**Symptoms:** The individual usually presents with back pain and then rapidly develops weakness. In children weakness starts slowly as they tend to trip easily and show difficulty climbing stairs. On examination individuals have usually lost their reflexes and are severely weak. Reflexes will be increased in those individuals who present with Axonal involvement. Some individuals will present with a purely sensory syndrome and this one is usually caused by small fiber involvement, which resolves with steroids (oral prednisone). Purely motor forms of GBS have also been reported, acute

motor axonal neuropathy (AMAN). The pure motor form of GBS usually has Serum anti-GM1b antibodies present, this group of individuals respond to IVIg but will not respond to plasmapheresis. GBS can be triggered by many different types of infection. It has been associated with Rocky Mountain spotted fever (RMSF). The individual initially presented with fever, rash, and an altered mental status, and he responded to therapy with **intravenous doxycycline**. Those individuals who have an altered mental status a search for an infecting organism should be done. Although doxycycline is the recommended therapy for children and nonpregnant women, chloramphenicol remains the recommended therapy for women during pregnancy. Identified infections associated with GBS, *Campylobacter jejuni* (23%), cytomegalovirus (10%), *Mycoplasma pneumoniae* (6%), and Epstein-Barr virus (3%). In some of these cases there will be a tendency to develop the chronic form of GBS called CIDP, in some there will be a poor recovery when the axon is damaged (axon is the central part of a nerve). Minocycline given early to the individuals can help to stop reoccurrence. Individuals treated with antibiotic have made an excellent recovery.

**Miller Fisher Syndrome:** (MFS) is a sub type of GBS in which individuals have difficulty in moving their eyes, double vision and loss of coordination. Individuals tend to complain of dizziness, they notice difficulty in moving their eyes. MFS starts out involving both eyes in most individuals, slowly progress to have complete immobilization of the eyeballs. Some develop pupillary sphincter paralysis and more than half have bilateral but often asymmetric dropping of eyelids (Ptosis).

**Test:** Antibodies to the ganglioside GQ1b are associated with Miller Fisher syndrome. They are not required for diagnosis which is based on clinical findings. Spinal tap shows a high protein content.

**Treatment** of GBS is by giving IVIG 500mg/kg per day for 4 days, and then 400mg once every 4 weeks till recovery. Detailed treatment plans are discussed under CIDP section. The cause of both these disorders is the same, an autoimmune attack against the Myelin, which is the covering around the peripheral nerves. Thus we have grouped the treatment of GBS, CIDP, Miller Fisher Syndrome and autoimmune neuropathies together and later a special section is devoted to the treatment of children with these diseases. In general IVIg should be the first line agent for treatment of GBS.

Following the diagnosis of an autoimmune disease, a long term anti-inflammatory treatment plan should be made if continued inflammation is seen on tests like ESR. Please read the diet section for tips on reducing inflammation. In some cases the ESR may be normal and if there is no need to start a pharmaceutical agent, over the counter supplements like aspirin, fish oil or Colostrum can be used. Aspirin is an anti-inflammatory medication and helps to reduce inflammation in all autoimmune disorders. If it is taken long term it may help reduce recurrent attacks of the disease. Fish oil (Cod Liver oil) also helps in reducing inflammation while providing the body with eicosapentaenoic acid (EPA) and

docosahexaenoic acid (DHA). Colostrum derived from cows, it's the pre milk secreted after pregnancy. Colostrum has powerful anti-inflammatory properties and has shown promise in long term management of autoimmune neuropathies. People have used a dose of 500mg twice a day minimum can be adjusted upto 2000mg daily.

**Non CIDP-Autoimmune neuropathies:** Caused by infections but present with unique clinical features

**Leprosy and autoimmune neuropathy: Leprosy** (Hansen's disease). Leprosy which is caused by a Mycobacterium lepra initially causes a neuropathy, through a mechanism called molecular mimicry. Autoimmune involvement in Leprosy, involves nearly every organ in the body starting from the scalp, eyes to the feet. In neurological cases it has caused bells palsy (dropping of the face), GBS (sudden nerve paralysis), and vasculitis (inflammation of blood vessels). Leprosy can occur with myasthenia, SLE and antiphospholipid syndrome. Leprosy is the oldest autoimmune disease that attacks the nervous system, the most common cause of polyneuropathy worldwide.

**Symptoms:** Individuals present with cuts or injuries on hands and feet coupled with loss of sensation. Sensory loss starts at the fingers and toes and may only affect a small patch of skin. Loss of sensation can lead to unnoticed injuries which also become infected. A variety of skin lesions are seen like macules (flat), papules (raised). Usually the skin lesion is less pigmented than the surrounding normal skin. Sometimes the lesion is reddish or copper colored, seen on the front and back of the body. Some individuals present with a stuffy nose.

**Test:** Positive skin smears: In some cases, rod-shaped, red-stained leprosy bacilli, which are diagnostic of the disease, may be seen in the smears taken from the affected skin when examined under a microscope after appropriate acid –fast staining.

**Treatment:** All cases are treated with dapsone, corticosteroids, and rifampin in combination if there is any progression of symptoms the dose of steroid need to be increased. In chronic pain cases CIDP treatment guidelines should be followed.

**Syphilis:** Tabes dorsalis is a degeneration of the nerve cells and nerve fibers that carry sensory information from the legs to the brain. The degenerating nerves are in the dorsal columns of the spinal cord (the portion closest to the back of the body) and carry information that help maintain a person's sense of position. Tabes dorsalis is the result of an autoimmune response to syphilis infection. Symptoms may take many years to appear after the initial infection. The autoimmune phenomenon called Tabes-dorsalis is only seen in syphilis, which is described here. Treponema Pallidum the causative agent of syphilis has never been discovered in any biopsy done on the posterior columns. Serum and CSF antibodies have been reported positive in TD against Treponema pallidum. This makes a case for molecular mimicry in TD against the spinal cord.

**Symptoms: Lancinating pain** (lightning like, appearing suddenly, spreading rapidly, and

disappearing) often is an early symptom and requires treatment. Neurologic presentation is one of ongoing loss of pain sensation, loss of peripheral reflexes, impairment of vibration and position senses, and progressive ataxia. Bladder incontinence and loss of sexual function are common. This constellation of symptoms is described by the mnemonic "PARESIS": **p**ersonality disturbances, **a**ffect abnormalities, **r**eflex hyperactivity, **e**ye abnormality, **s**ensorium changes, **i**ntellectual impairment and **s**lurred speech. The ocular abnormality is manifested as Argyll-Robertson pupils (small, irregular pupils bilaterally, nonreactive to light but reactive to accommodation). While syphilitic meningitis can develop in tertiary syphilis, it more commonly occurs in earlier stages of the disease.

**Diagnostic Test:** a screening RPR / VDRL test. Is confirmed by FTA-ABS

**Treatment:**

- Procaine penicillin 1gm I.M. daily for 21 days (with 1gm probenecid orally daily).
- Doxycycline 100mg t.d.s for 21 days.
- benzyl penicillin 2-4 gm I.V. every 4 hourly for 10 days
- Steroids are effective in controlling pain.
- Chronic cases are treated with treatment guidelines under CIDP.

**Facial palsy (Bells Palsy):** This is a sudden onset of temporary facial droop caused by inflammation and paralysis of the facial nerve. The inflammation in the facial nerve is autoimmune and can reoccur on the other side. A swollen facial nerve in the facial canal can be compressed. It can be an early manifestation of lymes disease. Usually the causative factor is herpes virus, cyto megalo virus or borrelia. Facial palsy is triggered by an exposure to cold air draft, reported commonly in London Taxi drivers and snow plough drivers around the world.

**Symptoms:** Symptoms range in severity from mild weakness causing a facial droop to total paralysis and may include twitching, weakness, or paralysis, drooping eyelid or corner of the mouth, drooling, dry eyes, impairment of taste, and excessive tearing in the eye. Facial palsy can occur on both sides when accompanied by Guillian Barre syndrome.

**Test:** Lyme titer, rheumatoid factor, erythrocyte sedimentation rate, antinuclear antibody, echocardiogram, fluorescent treponemal antibody absorption test, HIV titer, chest X-ray

**Treatment:**

- We recommend Minocycline 100mg daily for two weeks and one week of oral prednisone.(Minocin in areas of Lymes disease)
- Prednisone 1mg/kg/day tapered and stopped from one to two weeks
- Administer acyclovir (Zovirax) 800 mg PO 5 times/d for 10 d; 20 mg/kg in individuals younger than 2 years. Recent evidence supports HSV as the presumed cause in more than 70% of Bell palsy cases.
- It is recommended that some cotton wool be placed in the affected ear to reduce noise. Finally tinted glasses need to be used and the affected eye needs to be

patched and kept moist. Food may lodge in the mouth and will need manual removal. Rest is recommended until recovery results. Minocycline helps reduce inflammation, and if any *Borrelia* organism is present minocin will inactivate them.

**Dystonia:** Dystonia is defined as involuntary, sustained muscle contractions that can cause abnormal postures, twisting, or repetitive movements in any part of the body. Dystonias include:

- **Hemifacial Spasm**, (twitching of the face muscles or eye muscles)
- **Blepharospasm (eye closure)**
- **Meiges syndrome (facial spasm)**
- **Spasmodic torticollis (neck twisting)**
- **Writer's cramp** (difficulty writing and cramps with writing)

Some of the above dystonias can be autoimmune and be accompanied by other autoimmune conditions, these individuals have have elevated sedimentation rate & C-reactive protein and evidence of a preceding streptococcal infection. Antistreptolysin O titers should be obtained to confirm a recent invasive streptococcal infection. Other important antibody markers include antihyaluronidase, antideoxyribonuclease B, and antistreptokinase antibodies may be present. In one study 65% of adults with dytonia had Anti-basal ganglia antibodies (ABGA).

**Test:** Some dystonias can accompany SLE or M.S or Wilson's disease. Thus a MRI and spinal tap and ANGA can help diagnose these conditions.

**Treatment:** For strep induced dystonia look in PANDAS chapter, Botox is a approved and effective treatment for all dystonias. In MS and SLE induced dystonia steroids will be help.

**Diabetic Polyneuropathy & Diabetic Amyotrophy: Multiple studies in the last ten years have shown that diabetic polyneuropathy and amyotrophy are in reality a vasculitis (inflammation). These syndromes respond to anti-inflammatory treatments.**

**Here is a excerpt from Dr. king Engle at USC.** "Chronic Immune

Dysschwannian/Dysneuronal Polyneuropathy is an autoimmune peripheral-nerve and/or nerve-root disorder known to usually respond to intravenous immunoglobulin-G treatment. Benefit can involve any combination of motor-nerve fibers and large and small sensory-nerve fibers responsible for a progressively crippling, unbalancing, discomforting or painful disorder. "Diabetic neuropathy" is commonly considered untreatable. However, 81% of my 48 recently-summarized type-2 diabetes individuals with polyneuropathy, adequately-treated with intravenous immunoglobulin-G, off-label, were relieved, sometimes completely, of various motor and sensory symptoms, including pain, thereby resembling Chronic Immune Dysschwannian/Dysneuronal Polyneuropathy. Spinal fluid



protein in them is often elevated, higher values seeming to auger a better intravenous immunoglobulin-G response. Continuing the improvement requires continuing the intravenous immunoglobulin-G treatment, indicating both intravenous immunoglobulin-G responsiveness and dependency. The intravenous immunoglobulin-G responsive type-2 diabetes polyneuropathy usually is dysschwannian, sometimes mainly dysneuronal. IVIG is the most beneficial and safest treatment, is costly, but if intravenous immunoglobulin-G-treatability of a dysimmune component of type-2 diabetes neuropathy is overlooked, dismissed or rejected, as commonly happens, other costs are high regarding the individual's worsening morbidity and disability, and resultant need for increased medical care”.

We recommend that all diabetic neuropathy individuals be treated according to CIDP guidelines. IVIg is the preferred treatment seen in multiple studies.

**Autonomic Autoimmune neuropathy (pandysautonomia):** In this condition the small nerves controlling the function of the internal organs like the heart, blood vessels, stomach, intestines and the nerves controlling the amount of light entering the eye are affected. This type of nerve damage is called dysautonomia or pan-dysautonomia. The nerves which control the organ functions are collectively referred to as autonomic nervous system. Hypothalamus, is a small area in the brain that controls the autonomic nervous system. Autonomic means these nerves are not under our direct control they are independent. The autonomic nervous system (ANS) consists of two parts.

**Parasympathetic** (nerves which slow the heart and increase are intestinal motility) and **sympathetic** systems (nerves that accelerate the heart, constrict the blood vessels, open the airways and enlarge the pupil) are affected. When we get angry the hypothalamus in the brain triggers the parasympathetic nerves to raise the blood pressure and increase the hart rate as it prepares the body for a fight. (Remember to stay calm so we do not let the hypothalamus take over our life. A person, who is enraged, is under the control of hypothalamus)

The sympathetic (SNS) is referred as the "fight or flight" system, it has a stimulating effect on organs. The sympathetic constricts blood vessels, in intestinal tract and skin, while increasing muscle and lung blood flow. Bronchioles dilate allowing more oxygen to enter lungs. At the same time, the SNS increases heart rate, increases blood flow to the skeletal muscles and diverts blood away from intestinal tract. Sympathetic nerves enlarge the pupils and relax the lens, allowing more light to enter the eye. Sympathetic are stimulated by attraction, thus unconsciously dilating one's pupils makes the person looks more attractive. If you see other persons pupil dilate that means they are interested in you.

The parasympathetic nerves slows & relaxes the organs thus called the "rest and digest" response. Parasympathetic will dilate blood vessels to the intestines which helps in digestion of food, while slowing the heart rate it allows the body to rest. The airways (bronchioles) are tightened as the need for oxygen has diminished, constrict the pupils and

less light enter the eye. Dysautonomia is seen in CIDP with Involvement of the ANS.

**Symptoms:** Burning type pain in legs or arms with loss of hair has been. Small fiber loss will cause burning sensations. Localized increased sweating (hyperhydrosis) and eyelid drooping (Horner's syndrome). However, upon prolonged standing, autonomic failure can lead to loss of consciousness. Dysautonomic symptoms are frequent but are mild. Sexual dysfunction, hypertension, hypotension, asthma, syncope and heart arrhythmias

**Testing:** **Tilt test** has been abnormal most frequently. Check antibodies for Sjogrens, ANA for Lupus, Borrelia-antibodies for Lymes and anti-gliadin antibodies for Celiac-disease. Serum B-12 levels and H-pylori antibodies both these conditions can cause autonomic neuropathy. Voltage gated antibodies need to be checked for Eaton Lambert syndrome. Spinal fluid protein will be elevated in Guillain Barre and CIDP syndromes. A skin biopsy can be done to look for atrophy of autonomic nerve fibers.

**Treatment:**

- To prevent syncope (passing out spells) fludrocortisone, propranolol are used.
- Symptoms resolve slowly after **intravenous immunoglobulins** and prednisone.
- Treatment guidelines given under CIDP should be followed in new onset of AN. This condition has also responded to plasmapheresis.
- Celiac disease can present with similar symptoms and needs to be ruled for treatment look under the gastrointestinal chapter.
- If H-pylori antibodies are positive and B-12 levels are low look under the gastrointestinal chapter for treatment of these conditions.

**Holmes-Adie syndrome: (HAS) Ross syndrome & Harlequin syndrome:** These syndromes are autoimmune disorders resulting from a small fiber autonomic neuropathy involving the feet and a similar neuropathy involving the small autonomic nerve fibers to the eye. These syndromes can be triggered by injury, heat or infections. The disease can spread slowly if left untreated. This condition has been associated with Sjogrens and its antibodies are positive in HAS individuals, celiac disease is also an associated condition. In HAS one eye has a pupil that is larger than normal and constricts slowly in bright light (tonic pupil), along with the absence of deep tendon reflexes, in the ankles. HAS begins gradually in one eye, and often progresses to involve the other eye. At first, it may only cause the loss of deep tendon reflexes on one side of the body, but then progress to the other side. The eye and reflex symptoms may not appear at the same time. People with HAS can sweat excessively, usually only on one side of the body. The combination of these 3 symptoms – abnormal pupil size, loss of deep tendon reflexes, and excessive sweating – is called **Ross's syndrome**, which is a variant of HAS. Some individuals will have cardiovascular abnormalities, liver failure, gall stones due to reduced bladder motility. It is most often seen in young women. HAS is thought to be the result of inflammation and damage to neurons in the *ciliary ganglion*, an area that controls eye movements.

**Harlequin syndrome** is characterized by excessive sweating (hyperhydrosis) on one side and flushing, which are induced by heat or exercise. Usually, the sympathetic deficits confine to the face causing more sweating. Rarely, the cells in the ciliary ganglia are involved causing a mild eye lid droop. The unilateral facial flushing and sweating is induced by heat and exercise, observed on very close examination.

**Symptoms include:**

- **dilated pupil** in early stages
- decreased response to direct light reflex
- **tonic pupil:** pupil **slowly** constricts in bright light
- once the pupil has constricted it remains small for a long time (tonic pupil)
- decreased accommodation reflex ( takes a long time to focus)
- decreased tendon reflexes, individuals are often young women

**Tests:**

- Antigliadin antibodies to test for Celiac disease.
- Anti-SS-A and SS-B antibodies for Sjogrens,
- CRP and ESR, Borrelia antibodies for Lymes disease.

**Treatment:** These syndromes can be initial presentations of underlying autoimmune disease, and sometimes develop in poorly treated autoimmune disease individuals. If the disease is left untreated, these conditions can progress. New onset of these conditions can be part of a autonomic neuropathy which may respond to steroids. If Lymes serology is positive use Doxycycline and steroids.

**Reflex sympathetic dystrophy R.S.D or Complex regional pain syndrome:**

Complex regional pain syndrome or RSD is essentially inflammation of the autonomic nerves in a localized area. RSD has been associated with injury dating back to the Civil War. We have already described the association of autoimmune disorders with injury. In general, individuals who have complex regional pain syndrome suffer from pain, sensory changes, edema, sweating, and temperature disturbance in the afflicted extremity. Chronic changes can involve the skin, nails, and bone. Persistent inflammation, of the sympathetic nervous system and the central nervous system causes this condition. This is usually associated with CIDP.

**Symptoms:** (1) increased sweating, (2) color changes, (3) skin temperature changes, (4) weakness of the affected area (5) edema, (6) symptoms outside the affected dermatome.

**Treatment:** RSD, CRSP are caused by inflammation of the Autonomic nervous system. Many reports show individuals improved after steroid and IVIg treatments. Both of these conditions have developed in immunosuppressed individuals and promptly returned to baseline after reduction in immunomodulatory treatment. RSD has been reported with Lymes disease, herpes zoster virus, Parvovirus B19 and Campylobacter jejuni.

Please read the chapters on autonomic neuropathy and small fiber sensory neuropathy in the CIDP section. The treatment guidelines in the CIDP section should be followed.

**Palatal myoclonus (PM)** is a rhythmic contraction of the soft palate in the throat. When associated with eye movements, it is called "oculopalatal myoclonus". A clicking sound is commonly heard by the individual. The frequency of the jerking is ordinarily 1-2 hz. PM is the only movement disorder that persists during sleep. The inferior olive enlarges and develops rhythmic discharges when it is denervated by ipsilateral brainstem disease or contralateral cerebellar disease, and is responsible for the palatal myoclonus. PM may be stopped by neck position, or eliminated on mouth opening. Palatal myoclonus is a clinical diagnosis and since the inferior olive enlarges the possibility of inflammation is raised, in some cases GAD antibodies have been reported positive, which makes a relationship with autoimmune diseases.

**Tests:** that we recommend in all persons with palatal myoclonus:

- An imaging study of the brainstem with thin sections through the medulla.
- GAD antibodies, antigliadin antibodies

**Treatment:** Tegretol, Baclofen or Valporate may work.

**Trigeminal neuralgia (TN)**, also called *tic douloureux*, is a sudden jerk of the head due to pain. The pain causes, sudden burning or shock-like face pain that lasts a second followed by a pain free interval for a few minutes and can continue to reoccur in episodes. The intensity of pain is usually incapacitating. TN pain is typically felt on one side of the jaw or cheek. Episodes last for days, or weeks at a time and then can reoccur later. In the days before an episode begins, some individuals may experience a tingling or numbing sensation or a somewhat constant and aching pain. The attacks often worsen over time. The pain can be triggered by vibration or contact with the cheek (such as when shaving, washing the face) brushing teeth, eating, drinking, talking, or being exposed to the wind. TN occurs in people over age 50, and is more common in women than in men. TN is a presenting symptom in SLE, mixed connective tissue disorders and multiple sclerosis. Antibodies against anti-RNP are positive in these individuals. TN present with bilateral symptoms in these cases.

**Tests:** M.R.I. scans of the head to check for MS, tumor or any abnormal blood vessels around the trigeminal nerve. Anti-RNP antibodies need to be checked.

**Treatment:** If the MRI has ruled out vascular lesions then steroids are used which usually resolve the condition. Tegretol or Dilantin can be used for long term pain control.

**Treatment:** In early cases steroids need to be tried to suppress inflammation especially if GAD antibodies are present. Valporate can be used for long term but success is low.

**Amyotrophic lateral sclerosis (ALS) Autoimmune ALS:** Also called Lou Gehrig's disease after the famous Baseball player who fell victim to this disease. It is a progressive, fatal neurological disease that attacks the nerve cells (neurons) responsible for controlling muscles. In ALS, both the upper motor neurons and the lower motor neurons degenerate or die. ALS is caused by diverse etiologies, some are toxic exposures, injuries,

degenerative and some are autoimmune. Anti-Fas antibodies have been found in ALS individuals, increased titer against GM1-gangliosides, (AGM1-gangliosides) also seen in 20% of ALS individuals serum. Many other inflammation markers are increased in the disease. In one series 25 individuals with ALS were reported with IgG-subclass deficiency and T-cell deficiency. A study in Guam looking at pathogenesis of the diseases, showed intake of low calcium (Ca) and magnesium (Mg) and high aluminum water and of a plant excitatory neurotoxin as possible causes. In Italy increasing numbers of soccer players have developed ALS could be related to, use of illegal toxic substances or exposure to pesticides used on playing fields. Young individuals with HIV develop ALS which promptly responds to antiviral treatment.

Another theory is that ALS is caused by toxic levels of glutamate in the brain. Glutamate is a part of protein that cells in the body use to help break down food and build up body tissues. In the central nervous system, nerve cells (neurons) use glutamate to communicate with one another. Because too much glutamate can be toxic, the brain usually regulates the substance, keeping levels to those needed for body functioning. Abnormally high levels of glutamate have been found in the cerebrospinal fluid (the clear watery fluid that surrounds the brain and the spinal cord) of some individuals with ALS. In experiments, scientists have found that a protein responsible for removing excess glutamate from the brain appears not to work properly in people with ALS. They theorize that toxicity resulting from excessive glutamate might be killing motor neurons. The death of these cells leads to progressive muscle wasting in individuals with ALS.

**Symptoms:** The muscles gradually weaken, waste away and twitch, (fasciculation). Individuals with ALS lose their strength and the ability to move their arms, legs, and body. Muscles in the diaphragm and chest wall fail; individuals lose the ability to breathe. In most cases the disease does not impair a person's mind, a small percentage of individuals may experience problems with memory or decision-making, and there is growing evidence that some may even develop a form of dementia. They have emotional lability and tend to cry easily. There are no sensory symptoms.

**Tests:** A.L.S. individuals have been shown to have immunoglobulin sub class deficiency. Abnormalities in IgG subclass-1, and IgG subclass-3. Thus check for IgA levels, IgG levels and IgG-subclass levels.

**Treatment:**

- Many small studies have been reported where the use of **Minocycline** has shown some benefit in ALS individuals. A trial of Minocycline should be given to all individuals to reduce oligodendrocyte apoptosis (cell death), microglial/macrophage activation, improve functional outcome. Research studies with minocycline and Riluzole shows benefits.

Treatment with the neuroprotective drug Riluzole has previously been shown to increase the probability of survival in individuals.

- If IgG-subclass levels are low then they have immune deficiency and then IVIG should be tried if available. Rarely a M.M.F. case can present and look like ALS. There is the case of a individual in Massachusetts General Hospital who has a diagnosis of ALS and improved with IVIg. We have seen another individual who had an ALS diagnosis after receiving IVIg; he was able to get out of the wheelchair. Three studies have been reported on IVIg and ALS, none of the individuals improved in any of these studies.
- Stop all foods with Glutamate and increase the Magnesium in the diet. Please see the diet chapter for more information.

**Chronic Lyme disease and autoimmune dysfunction:** Lyme disease was first recognized in 1975 after a number of cases occurred in the same town in North America. It subsequently took its name from this town, which was called Old Lyme, in Connecticut. Lymes disease which is spread to humans by a small bug called the deer tick. This bug passes a spirochete called *Treponema Pallidum* to the human. Lyme borreliosis is due to infection with the spirochete *Borrelia burgdorferi*, and is associated with persistent infection unless treated with antibiotics. The persistent nature of infection by *B. burgdorferi* can lead to development of chronic autoimmune disease. A infectious diseases transforms into multiple autoimmune conditions.

Klempner did a study in chronic Lymes and found that chronic antibiotics did not change the course of chronic disease. Then NIH (National Institutes of Health) recommended that autoimmune basis of Lymes disease needs to be explored. Early cases which were treated with IVIg have had good success. A study by Recvhes showed that *B. burgdorferi* may share common epitopes which mimic self-proteins. Currently *Borrelia* antibodies have been associated with remitting relapsing Multiple sclerosis, Thyroiditis, carotid artery disease, epilepsy and arthritis.

**Symptoms:** Usually the first sign of Lymes infection is a circular skin rash at the point of entry. This can easily be overlooked. Followed by symptoms of tiredness, headache, joint pains, and flu-like symptoms may also occur. If not treated these symptoms may last for weeks, even months. As the disease progresses then shortness of breath, chest pains, weakness, and tingling numbness in the legs and arms starts. Some may start to notice memory problems, difficulty concentrating and fatigue.

**Treatment:** Acute Lymes is an infection. Once the disease has involved multiple organs or the nervous system it has become an autoimmune disease and immune suppressive treatments are required.

- Lymes with antimicrobial therapy, by using oral agents such as doxycycline or amoxicillin is successful among more than 90% of individuals. The intravenous Ceftriaxone is the drug of choice for severe acute and chronic infections and especially if neurological involvement is seen. Regardless of therapeutic agent,

there appears to a small minority of individuals (<10%) who do not respond; such cases may be due to long-term persistence of *Borrelia* cysts. Several other therapies are available, including hyperbaric oxygen therapy and immune system supplements. Austin was the first to report that *Borrelia* loses its infectivity at higher oxygen concentrations setting up the hyperbaric oxygen chamber treatments. Though there are no studies on the hyperbaric chambers but individual reports suggest that it does help cerebral and cortical symptoms.

- Steroids can also be used for immunomodulation, celiac diet should be tried and please follow the protocol in the diet page and for immunosuppressive treatment follow the CIDP protocol.
- Chronic Lyme individual who does not show any response to antibiotics should be treated with IVIg. If there is no response to IVIg then steroids and IVIg combination can be used. In resistant cases plasmapheresis can be tried. Please see the CIDP treatment section for all treatment options.

**Multiple Sclerosis:** Multiple sclerosis (MS) is a chronic, autoimmune disease in which immune system attacks the Myelin covering the nerves in the brain and spinal cord. This is similar to autoimmune peripheral neuropathy where the attack is against peripheral myelin. The Myelin in the Brain and spinal cord is made by cells called oligodendrocyte and in the peripheral nerves by cells named Schwann cells.

In multiple sclerosis, after exposure to infections like (Epstein-Barr virus (EBV), *Chlamydia pneumoniae*, *Borrelia*), the body incorrectly directs antibodies and white blood cells against proteins in the myelin sheath, which surrounds nerves in the brain and spinal cord. This causes inflammation and injury to the myelin-sheath and ultimately to the nerves that it surrounds. This damage results in multiple areas of scarring (sclerosis). Eventually, this damage can slow or block the nerve signals that control muscle coordination, strength, sensation and vision. This damage can be visualized by a M.R.I. scan as multiple white spots in the brain. There are some high risk areas in the world where the incidence of M.S. is higher. These areas include Northern United States, United Kingdom, Finland, Canada and New Zealand. The high risk areas, on the world map, lie between 45 degree North and 60 degree north. The area of the world below 45 degree south also has a higher incidence of MS. Children born in high risk areas show a higher incidence of MS. Lower amount of Sun light in the high risk areas may result in lower amount of Vitamin-D. A historic study was published by workers at the Vanderbilt School of Medicine showed CSF samples from individuals with relapsing-remitting MS, having increased CSF antibodies to *C. pneumoniae*.

### Types of M.S

- **Relapsing remitting.** This type of MS is seen in 90% of the cases characterized by relapses (disease flare-ups), followed by periods of remission. This is the most common type. We have seen many cases where the individual was labeled as progressive MS only to find they had clear history of remissions and relapses.

- **Primary progressive.** People with this less common form of MS experience a gradual decline, without periods of remission. People with this form of MS are usually older than 40 when symptoms begin.
- **Secondary progressive.** More than half the people with relapsing remitting MS eventually enter a stage of continuous deterioration referred to as secondary progressive MS.
- **Progressive M.S.** Progressive downhill course.

#### Symptoms of M.S. are:

- Numbness or weakness which typically occurs on one side of the body.
- Double vision, blurring of vision or sudden loss of vision.
- Tingling numbness or pain one half of the body.
- Electric-shock sensations that occur with certain head movements
- Tremor, lack of coordination or unsteady gait and weakness.
- Fatigue specially after exposure to heat, or exercise.
- Dizziness or feeling of spinning.

#### Tests:

- **M.R.I.** Scan can confirm the diagnosis of M.S. which shows multiple white spots.
- **Spinal tap:** increased white cells and increased proteins with oligoclonal bands.
- CSF should be tested CSF antibodies to *C pneumoniae.*, **Borrelia**, **Chlamydia**, **H. Pylori**, **Acinetobacter** , **Pseudomonas bacteria**, and **Gluten**.(antgliadin antibody)
- **Plasma homocysteine** levels can be elevated. Serum calcium & vitamin D levels, Serum Vitamin B-12, thiamine and B-6 levels.

#### Treatment:

- **Minocycline** is a potential therapy for M.S it has been shown to reduce lesions on the MRI scan. Minocycline is a tetracycline antibiotic Treatment: Minocycline 100 mg at night (Monday, Wednesday, and Friday). Minocycline treatment should be tried for at least two months at least to get rid of Chlamydia, Borrelia if this helps try for 2-3 months. Treat according to antibody results. Try eliminating the infection first based upon the antibody results)
- **Diet:** If antigliadin antibodies are present then a two to three month trail of a diet on milk, rice, meat, chicken, fish, vegetables and fruits need to be tried to se if any benefits result. Please read the diet section for more information. Vitamin D replacement with cod liver oil should benefit all individuals. Vitamin B12 sublingual supplements are also beneficial.
- **Methylprednisolone (Solumedrol):** Is used to reduce inflammation in a new attack of **M.S.** One gram of methylprednisolone reconstituted in 16 cc of sterile water and add to 150cc of 0.9% NS. Infuse over 1.5 hours. If Methylprednisolone is not available: Decadron 20mg: 5cc of Decadron 4 mg/ml solution put 50 cc of 0.9% NS. Infuse over 30 minutes.



- **Beta interferons.** Interferon beta-1b (Betaseron) and interferon beta-1a (Avonex, Rebif) are genetically engineered copies of proteins that occur naturally in the body. They help fight viral infection and regulate your immune system. Betaseron is injected under your skin (subcutaneously) every other day. Rebif is injected subcutaneously three times a week. Avonex is self-injected into the muscle (intramuscularly) once a week. These medications reduce flare-ups of MS. Beta interferons should never be used in combination with one another. Only one of these medications should be used at a time.
- **Intravenous Immunoglobulin (IVIg)** Some new studies have shown that IVIg given early in the treatment of M.S will help delay the disease onset and provide a long term remission. The dose is 500mg/kg/day for four days. Has to be repeated for 5-6 months.
- **Muscle relaxants.** Baclofen and tizanidine (Zanaflex) are oral treatments for muscle spasticity. Baclofen often increases weakness in the legs. Zanaflex appears to control muscle spasms without leaving your legs feeling weak but can be associated with drowsiness or a dry mouth.
- **Medications to reduce fatigue.** To help combat fatigue, the antiviral drug amantadine (Symmetrel) 100mg once a day has been used.
- **Plasma exchange (plasmapheresis).** Plasma exchange may help restore neurological function in people with sudden severe attacks of MS-related disability who don't respond to high doses of steroid or IVIg treatments. For a list of all other drugs please see the CIDP treatment section.

**Lambert-Eaton Myasthenic Syndrome:** Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune paraneoplastic syndrome producing antibodies against presynaptic voltage calcium channels. Some of the individuals have an underlying malignancy, particularly for small cell carcinoma of the lung. A search for chest cancer should, therefore, be made in individuals with newly diagnosed Lambert-Eaton syndrome, and should be repeated at intervals during the first years after the onset of symptoms.

**Symptoms in LEMS:** The individual complains of weakness and pain, initial short increase of the muscle strength after exercise is seen followed by weakness and fatiguability. The proximal muscles, especially the (thigh, pelvis, shoulders, arms) appear weak and unsteady gait are commonly observed, early in early disease. Rarely, mild degree of ptosis, weakness of facial muscles difficulty is swallowing and talking (Bulbar weakness). Some individuals can have reduced Muscle tendon reflexes, which may increase after activity or exercise. Dysfunction of the autonomic nervous system is also common, which may be manifest as visual disorder (blurred vision due to impairment of accommodation in the pupil), dry mouth, sexual impotence due to erectile dysfunction or constipation are all due to autonomic dysfunction.

**Test for LEMS:** X-Ray chest, CT or MRI imaging scan of the chest may be supplemented

by sputum analysis and bronchoscopy (all these tests are done to search for a tumor). A serum test for voltage-gated calcium channel antibodies (anti VGCA antibodies). Electrophysiological testing shows a small compound muscle action potential and improvement in size of the action potential with exercise.

**Treatment in LEMS:**

- The individual improves after removal of the cancer. If there is no improvement, particularly in individuals without tumor. Then immunosuppressive therapy with prednisolone and azathioprine usually help control symptoms. In some cases even remissions have been reported.
- IVIG and Plasmapheresis are an effective treatment for individuals with severe symptoms. 4-Diaminopyridine (possibly in combination with pyridostigmine) seems to be ideally suited for the symptomatic treatment of the Lambert-Eaton syndrome. It enhances the release of acetylcholine from the presynaptic nerve terminals.

**Myasthenia Gravis: Grave means serious:** Myasthenia gravis is a chronic autoimmune neuromuscular disease characterized by weakness of the voluntary (skeletal) muscles of the body. The name myasthenia gravis, means "grave muscle weakness." The hallmark of myasthenia gravis is muscle weakness that increases during activity and improves after of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often, involved in the disorder. The muscles that control breathing, neck movements and limb movements may also be affected. When a nerve impulse travels down the nerve, a chemical neurotransmitter called acetylcholine is released in the nerve ending and travels to acetylcholine (Ach) receptors located on the muscle side of the synapse, causing the muscle to contract. Among people with myasthenia gravis, this normal impulse transmission of Ach is disrupted by autoantibodies that target the body's own Ach- receptors and block them. If enough receptors are blocked by autoantibodies, then the muscle contraction will be weak, causing the symptoms of myasthenia gravis.

Many pesticides contain organophosphorus chemicals that can inhibit the acetylcholinesterase enzyme and make myasthenia worse. Halides (like **chlorine** and **fluorine**) may pose additional risk for myasthenia gravis individuals. In one case report, an individual was exposed to chlorine gas and subsequently developed generalized myasthenia gravis). Fluoride is also implicated, and fluoridated water may trigger a myasthenia gravis crisis or contribute to long-term deterioration, with extreme exhaustion and muscle weakness

**Symptoms: Dropping eyelid or double vision,** are the initial symptom of myasthenia gravis in two-thirds of individuals. If both the eyelids are drooping it is difficult for the physician to notice this. Difficulty chewing, swallowing, or talking, is the initial symptom

in some individuals, and limb weakness is rare. Initial weakness is rarely limited to single muscle groups such as neck or finger extensors or hip flexors. The severity of weakness fluctuates during the day, usually being least severe in the morning and worse as the day progresses, especially after prolonged use of affected muscles. Some individuals just have ocular Myasthenia, they can present just with double vision.

- **Diagnosis of Myasthenia**

**Ice test.** After covering the individual's eye with an icepack for a couple of minutes, the physician will look for improvement in eyelid drooping. Any improvement may point toward a myasthenia gravis diagnosis.

- **Tensilon Test.** As acetylcholine receptors are blocked in myasthenia gravis, drugs that increase the amount of acetylcholine can be used, to test for the disease.

**Edrophonium** is a fast-acting acetylcholinesterase inhibitor that, when administered intravenously, will produce immediate and temporary relief of muscle weakness in myasthenia gravis individuals by sparing existing acetylcholine. Edrophonium onsets quickly (30 seconds) and lasts for only about five minutes. If the individual has an eyelid droop, then you give 8mg of Edrophonium, in a positive test the eyelid will rise up to its normal position.

- **Antibodies:** Antiacetylcholine receptor antibodies are detectable in the serum of about 80 percent of people with myasthenia gravis. However, they are present in only about 60 percent of people with symptoms that are confined to the eye muscles. In cases which involve swallowing (bulbar muscles) muscle-specific kinase (MuSK) antibodies are seen.
- **Electrophysiological studies.** The amplitude of the compound muscle action potential (CMAP) obtained by repetitive nerve stimulation (RNS) is normal or slightly reduced in individuals without MG. The amplitude of the fourth or fifth response to a train of low frequency nerve stimuli falls at least 10% less from the initial value in myasthenic individuals. This decrementing response to RNS is seen more often in proximal muscles, such as the facial muscles, biceps, deltoid, and trapezius than in hand muscles. A significant decrement to RNS in either a hand or shoulder muscle is found in about 60% of individuals with myasthenia gravis.
- **Thymus Tests:** An X-ray of the thymus can be done to look for enlargement. A C.T scan or MRI scan can show a tumor within the thymus. Some people with myasthenia gravis suffer from some form of abnormality in the thymus gland. The thymus gland is where T cells the chief immune cell involved in myasthenia gravis are produced. About 70 percent of people with myasthenia gravis have an enlarged thymus gland (hyperplasia), and 20 percent have (usually benign) thymic tumors called thymomas
- **Thyroid Tests:** Hyperthyroidism and hypothyroidism can be associated with increasing myasthenic weakness (Need to test TSH, T3-T4)

### **Treatment of Myasthenia:**

- **Acetylcholinesterase inhibitors:** These drugs work by blocking the enzyme that normally destroys acetylcholine in the synapse, which allows the existing acetylcholine more time to interact with the available receptors. (**Pyridostigmine 60mg three times** a day or neostigmine).
- **Thymectomy:** Surgical removal of the thymus gland, following a thymectomy, individuals often report that symptoms lessen and, in many cases the disease disappears completely.
- **A new simpler way of doing Thymectomy** has been reported. CT-guided percutaneous ethanol injection is a minimally invasive alternative treatment for myasthenia gravis. 22-gauge needle is inserted into the thymus under CT guidance, and then ethanol is injected step by step until it is distributed throughout the whole thymoma, the normal thymus. The amount of ethanol injected ranges from 2 to 13 mL, with a mean of 7 ML. Follow-up at 3-4 weeks shows that the thymus or thymoma has completely necrotized. (A 5-year follow up study showed that the condition markedly improved in 35 individuals.) (AJR Am J Roentgenol. 2003 Sep; 181(3):721-4.Wang P)
- **Plasmapheresis:** Plasmapheresis separates plasma, which contains the autoantibodies, from red blood cells, which are then returned to the body. This treatment improves symptoms temporarily and is especially valuable in preparation for surgical removal of the thymus. Several studies have reported that plasmapheresis is tolerated well in individuals. The most common side effects are reversible hypotension (low blood pressure) and mild tremor.
- **Intravenous immunoglobulin:** High-dose intravenous human immunoglobulin (IVIg) has emerged as a therapy for various neurologic diseases, including myasthenia gravis. Studies that compared plasmapheresis and IVIg found that the improvement had a more rapid onset after plasmapheresis than after IVIg. During pregnancy only IVIg is the only drug to be used.
- **Immunosuppressants:** Please see treatment guidelines under CIDP. High-dose cyclophosphamide is an effective alternative in individuals with refractory disease.

**Drugs to be avoided in Myasthenia:** The adverse effects of many medications may provoke exacerbations. Some of the medications reported to cause exacerbations of MG include the following:

1. **Antibiotics** – Macrolides (erythromycine, zithromax), fluoroquinolones, aminoglycosides, tetracycline, and chloroquine
2. **Antidysrhythmic agents** - Beta-blockers, calcium channel blockers, quinidine, lidocaine, procainamide, and trimethaphan
3. **Miscellaneous** – Diphenylhydantoin (Dilantin), Lithium, chlorpromazine, muscle relaxants, Penicillamine, levothyroxine, adrenocorticotrophic hormone (ACTH), and, paradoxically, corticosteroids. Riluzole, intravenous iodinated contrast, Amitriptyline, Artane & Timolol.

**Stiff-Person Syndrome:** Stiff person syndrome (SPS) shows fluctuating muscle stiffness in the back, arms and legs. The first symptom is a persistent stiffening of the back or a limb which may be worse under stress. A sensation of aching or stiffness may be noted.

This progresses with time and is described as stiffness. Additionally individuals experience spasms of the involved muscles which are severe, and painful. People develop startle, a heightened sensitivity to stimuli such as noise, touch, and emotional distress. Startle, can set off muscle spasms, sudden jerking or falls. Abnormal hyperextended posture is characteristic in SPS also called the lordotic posture and rarely a flexed hunchback type posture is seen. Some SPS individuals have difficulty walking and walk with small stiff, steps and tend to trip easily, loud sound can cause spasms. Many people are kept awake and in pain by dogs barking in the night. Some people arch over in an opisthotonic (backward bending attack with the head and heels touching the bed and rest of the body arched above the bed) this posture is very painful and can last hours at a time, relieved by sleep. SPS affects **twice as many women** as men. It is frequently associated with other autoimmune diseases such as diabetes mellitus (DM), thyroid disease, vitiligo, pernicious anemia, adrenal insufficiency. Glutamic-acid decarboxylase antibodies are present in one quarter of the individuals. Half of the individuals will become wheel chair bound, despite treatment.

**Symptoms:** There are painful muscle spasms and the individual is sensitive to sudden movement or stimulation. The stiffness of the muscles subsides during normal sleep.

- Constant painful muscle spasms back, abdomen, legs arms and neck.
- Stiff-legged gait, short steps, trips easily
- Slow eye movements, Shortness of breath
- Hunched posture or a hyper extended posture (lumbar hyperlordosis).
- Difficulty making sudden movements

**Tests:**

- Positive anti-GAD (glutamic-acid decarboxylase antibodies )
- Borrelia antibody in CSF (may be positive)
- Electromyography (EMG) - Characteristic continuous motor unit activity at rest is especially prominent in the paraspinal muscles. Activity resolves with sleep and disappears with diazepam.

**Misdiagnosed as:** Parkinsons, multiple sclerosis, fibromyalgia, anxiety disorder.

- **Treatment:** These individuals respond to prednisone, azathioprine, with long acting benzodiazepines (Ativan, clonazepam, Valium), Baclofen, Some individuals show a good response **IVIG** and rarely plasmapheresis. **Physical therapy** is very important to try to stretch the joints and improve the range of motion. In those individuals who show no response to any treatment an intraspinal **Baclofen pump** helps control muscle spasms. Antibiotic treatment with Minocin or doxycycline needs to be tried, as some cases can be secondary to Borrelia infections.

- SPS with Thymoma has been reported which resolved with Thymus removal.
- If you see that the usual treatments are not helping the individual then it is time try Magnesium supplement at 400 mg three times a day. Celiac diet should also be tried. See the diet section. Fish oil up to 1 gram daily with an Asprin should be used by all individuals unless there are contraindications like stomach ulcers or bleeding disorders which can get worse by using Asprin.

**Sydenham Chorea.** Sydenham's chorea is generally regarded as an inflammatory complication of Group A beta hemolytic streptococcal infection, the disease is more common in females than in males and in childhood. In adolescence, the affected populations are composed almost entirely of females. Sydenham's chorea has a post-streptococcal autoimmune etiology appear to arise from targeted dysfunction of the basal ganglia. PANDAS (**p**ediatric **a**utoimmune **d**isorders **a**ssociated with streptococcal **i**nfections) are the acronym applied to a subgroup of children with obsessive-compulsive disorder or tic disorders occurring in association with streptococcal infections. Recent reports show dystonia, chorea encephalopathy, and dystonic choreoathetosis occurring as sequelae of streptococcal infections.

**Symptoms:** After streptococcal infection, the interval of symptom onset and chorea is a few months, with arthritis or carditis. The individual develops quick, purposeless, nonrepetitive, involuntary movements that disappear with sleep and may involve all except the ocular muscles. Voluntary movements are abrupt and jerky, with impaired coordination. Facial grimacing is common.

**Test:** Throat culture should be done on all children, anti-deoxyribonuclease B (anti-DNase B) and anti-streptolysin O (ASO) titers. Antibasal ganglia antibodies (ABGA) are associated with Sydenham's chorea and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

#### **Treatment of chorea.**

- Benzathine penicillin G in a monthly IM injection of 1.2 million U is effective, including penicillin G 400,000 U divided bid or penicillin V 250 mg divided bid. Sulfadiazine, in a single oral dose of 1 g/day or 500 mg/day in individuals who have weight less than 50 lbs., is as effective as other oral regimens.
- To suppress inflammation aspirin or prednisone should be used. Two different studies have reported, nine individuals severe chorea and two with neuroleptic-induced Parkinsonism were treated with pulse steroids and oral prednisone for two-seven months with major improvements.
- The National Institutes of Health reported using IVIg in chorea individuals with 70% reduction in the symptoms. With plasmapheresis the reduction in symptoms of chorea was 50%; with steroids 30% reduction in chorea symptoms was seen.

**Parkinson also has a autoimmune etiology and respond to immunomodulation:**

Parkinson's disease (PD) is a progressive disorder that affects nerve cells (neurons) in the brain that help controls muscle movement. This group of nerve cells (substantia nigra) makes dopamine, a chemical which is used for transmitting signals from brain cells to facilitate movements. By the time PD symptoms appear, 70 to 90 percent of dopamine producing cells have been lost. This disease is caused by diverse causes, some of which are immune mediated. Recently increased iron levels in the substantia nigra have been reported. Pesticides exposure has been associated with development of Parkinsonism. Amateur gardeners were 9 percent more likely to suffer from the disease than non-pesticide users. Farmers were 43 percent more likely to develop Parkinsons. Rotenone (pesticide) has been associated with an effect on dopamine neurons that are located in the brain stem. In rural Fairfield, Montana Parkinson's disease occurrences are much higher than the national average of 1 in 1000, At least 12 people living around the Fairfield area, with a population of 650, have contracted the disease. University of Calgary and the University of Saskatchewan tested the hypothesis that the occupational use of herbicides is associated with an increased risk for Parkinson's disease. Recently a number of studies have also shown that H-pylori infection is common in Parkinson individuals. Some of these cases in late stages were treated with H-pylori eradication and a U-turn of the disease was seen. In another group the treatment was stopped as they did not see improvement. There is one benefit from Parkinson's that individuals do not get any wrinkles as they cannot smile. Several autoantibodies and disturbances in T-cell function have been found in PD. The theory proposes that the production of autoantibodies and T-cell activation are important in the pathogenesis of idiopathic PD. The autoimmune destruction of the substance P input leads to a secondary loss of the dopaminergic system and hence PD. Autoimmune Parkinsons is seen following transplant surgery, after immunosuppression, following infections. SLE has been associated with Parkinson's disease, in three case reports the disease reversed with the use of IVIg treatment. Half of individuals with PD have abnormal levels of anti-Fas antibodies and Anti-GAD antibodies

**Causes** of Parkinsonism include:

- § Lacunar strokes can be vasculitis. (Inflammation)
- § Encephalitis, inflammation of the brain usually caused by infection
- § Lyme disease, Epstein Barr Virus (Inflammation)
- § Progressive supranuclear palsy, a rare degenerative brain disorder
- § Multiple systems atrophy, a degenerative disorder that destroys the nervous system
- § Corticobasal degeneration, a rare neurological disease
- § Chemical exposure and medications, such as some antipsychotics
- § Autoimmune diseases like SLE. (Inflammation)

**Signs** and symptoms of Parkinsonism include:

- § Tremors at rest, pill rolling type.
- § Flexed posture, Slowed movements
- § Impaired speech , small handwriting
- § Muscle stiffness, reduced smiling, **no wrinkles** (khans sign)
- § Loss of automatic movements such as blinking

**Tests:** There are no tests for Parkinsons disease. CT scan of the head can be done to look for strokes. H-pylori antibodies, Borrelia antibodies checked in individuals to see if they are carriers of the infection. ANA and CRP can be checked specially in women to look for Lupus.

**Treatment:**

- **Sinemet** 25/100 three times a day and amantadine 100mg a day are used to treat the symptoms of regular Parkinsonism. We would like to concentrate on the treatment of autoimmune Parkinsonism which results in individuals with SLE, Post infectious, drug induced or following transplantation of organs.
- Two girls with SLE, who developed Parkinsonism which did not respond to prednisone and cyclophosphamide, recovered with IVIg.
- In post Viral Infections induced Parkinsonism, steroids and IVIg work well. In Lymes disease associated Parkinsonism steroids are to be used.
- Co enzyme Q-10 based on past studies shows a benefit at 300 mg to 1200mg daily dose taken with vitamin E.

**Paraneoplastic Autoimmune Syndromes:** People with cancer may develop problems with the brain, spinal cord or nerves, even though their cancer has not spread to the nervous system. Paraneoplastic syndromes are a group of autoimmune disorders that are triggered by a person's immune systems response to cancerous cells. Paraneoplastic syndromes occur when cancer-fighting antibodies or white blood cells known as T cells mistakenly attack normal cells in the nervous system. These disorders typically affect middle-aged to older persons and are most common in persons with lung, ovarian, lymphatic, thymus, testicular or breast cancer. Following twelve types are usually seen.

- **Autonomic dysfunction** Abnormal pupil response, Constipation, Impotence, Orthostatic hypotension (dizzy feeling on standing up), Sweating abnormalities
- **Brainstem encephalitis** Dizziness (vertigo), Difficulty swallowing, No eye movements (Ophthalmopelgia), eyes move back and forth (Oscillopsia), slurred speech (Dysarthria)
- **Cerebellar degeneration** Dysarthria, Clumsy Gait (ataxia), quick eye movement (Nystagmus). Anti-Yo or anti-Purkinje cell antibody may be present.
- **Focal cortical encephalitis:** Depression, Anxiety, Seizures, Confusion.



- **Lambert Eaton Myasthenic Syndrome (LEMS)** Proximal Muscle weakness (Hip weakness fatigue, Reduced or absent muscle reflexes).
- **Limbic encephalitis** confusion, recent memory loss, depression, hallucinations, Seizures (can be non convulsive, PLEDs). Anti-Hu antibodies are present.
- **Myelitis:** Inflammation of the spinal cord causing weakness, numbness in limbs.
- **Opsoclonus/myoclonus:** Myoclonic (brief, shock-like muscle spasms), and Opsoclonus (irregular, rapid eye movements). Anti-Ri antibodies may be present.
- **Retinopathy** Night vision problems, Photosensitivity, Visual loss,
- **Sensory neuropathy:** Numbness in the feet which spreads to ankles and knees, deafness, pain similar to described under tabes-dorsalis, altered taste and smell. Anti-Hu antibodies may be present.
- **Morvan's chorea :** neuromyotonia, (muscle cramping) and myokymia (muscle twitching)), dysautonomia ( syncope, severe constipation, and urinary incontinence), hyperhidrosis (excessive sweating) of the trunk and limbs, weight loss, impairment of recent memory, anxiety, and restlessness, severe insomnia, visual hallucinations, pruritis with atopic dermatitis.
- **Stiff person syndrome:** Muscle stiffness (look under Stiff person syndrome chapter for details and Antibodies directed against amphiphysin may be present)
- **Lateral amyotrophic syndrome (LAS)** weakness and atrophy and hyperreflexia with fasciculations (muscle twitching). This form of LAS differs from the nonparaneoplastic form as it includes sensory loss involving (loss of joint position sense or proprioception and inability to feel vibration or pallesthesia).

#### Tests:

- ESR and CRP are usually elevated and a search for a tumor may show a lung, abdominal or thymus tumor.
- Serum antibodies are present in many cases and generally tests for paraneoplastic antibodies may show their presence.
- A search of the tumor by a MRI scan, chest X-ray and endoscopies of the stomach and intestines are recommended.
- Tumor markers are very useful for diagnosis of cancers that are clinically silent, but most markers are not specific for determining the origin of the cancer. For example, CEA (carcinoembryonic antigen) is increased in individuals with tumors of the breast, lung, and digestive tract, as well as in individuals who are heavy smokers. On the other hand, prostate-specific antigen (PSA) is increased only in individuals with prostatic disorders, whether benign (including inflammatory diseases) or malignant.

**Treatment of Paraneoplastic Syndromes:** Treatment with plasmapheresis, IVIG of 500mg/kg given daily for four days or steroids is initial treatment which may help control the symptoms. A search for a malignant tumor should be made in all these cases and the removal of the tumor will cure these syndromes. If autoantibodies are detected, the best drug to use may be cyclosporine. For long term use azathioprine is effective in controlling the diseases.

**Neuro-Myotonia: Isaac's syndrome or continuous muscle fiber activity syndrome:**

NeuroMyotonia is a rare disorder in which continuous fine repetitive muscle movements called (myokymia) are seen. Muscle weakness can be present. Muscle relaxation may be difficult especially after physical activity involving the particular muscle. Continuous activity in the motor neurones activates the peripheral nerve fibers that activate these fine muscle movements.

**Symptoms of NeuroMyotonia:** Which include progressive muscle stiffness, continuous vibrating or twitching muscles, cramping, increased sweating, and delayed muscle relaxation, occurs even during sleep or when individuals are under general anesthesia. Many individuals develop reduced reflexes and muscle pain, but numbness is relatively uncommon. Symptoms can be limited to twitching of eyelids, facial muscle spasms. In most individuals stiffness is most prominent in limb and trunk muscles, they have difficulty walking and continuous rippling in muscles of upper and lower limbs is seen. Speech and breathing may be affected if pharyngeal or laryngeal muscles are involved. Involuntary flexion of ring and little finger with associated pain in the elbows is also seen.

**Tests in NeuroMyotonia:** EMG test shows, Myokymic discharges in involved muscles (spontaneous firing of single motor units as doublet, triplet or multiplet discharges at irregular intervals) sounds like marching soldiers. Nerve conduction study can show neuropathy. Blood counts, chemistry, thyroid profile, Rh factor need to be checked and are usually normal. CPK is raised. CSF shows elevated protein and lymphocytes. Voltage-gated K<sup>+</sup> channel antibodies can be present.

**Treatment of NeuroMyotonia:** Steroids are first line of treatment. Plasmapheresis, IVIg and immunosuppressive drugs can be used. Please see guidelines in CIDP section.

**Moyamoya disease (MMD):** is a rare, progressive cerebrovascular disorder caused by blocked main arteries at the base of the brain. The name “Moyamoya” means “puff of smoke” in Japanese and describes the look of the tiny vessels formed to compensate for the blocked arteries. Individuals suffer from recurrent TIA or mini strokes. It can occur in any age in some individuals it is associated with the antiphospholipid-antibody. In these cases if early anticoagulation or aspirin treatment is given there is complete remission. MMD is also associated with Down's syndrome.

**Symptoms of Moyamoya** include vision problems, weakness, numbness and difficulty

speaking, seizures and paralysis.

**Tests for Moyamoya:** Cerebral angiography shows the typical findings of MMD, with occlusion of both internal carotid arteries at the base of the brain, coupled with abnormal new collateral vessels. **Antiphospholipid antibodies** can be present, Vitamin B1, B6, B12, and Homocysteine levels should be checked, vitamin levels can be low with high homocysteine levels suggesting inflammation. CRP levels are elevated showing inflammation. Protein C (PC) and its cofactor, protein S (PS) need to be checked as they can be low.

**Treatment of Moyamoya:**

- Warfarin and Heparin anticoagulation helps reverse disease progression if anticardiolipin antibodies are found. A case has been reported with Mycoplasma Pneumonia infection.
- Individuals with progressive disease are helped by superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis. In individuals with Moyamoya disease, nicardipine has a beneficial effect on cerebral hemodynamics and may prevent ischemic sequelae by optimizing existing collateral circulation in postoperative individuals.

**Autoimmune Migraine:** Migraine as a disease affects approximately 35 million Americans, most of whom are women, with up to 38 million Americans having Migraine. These painful headaches are preceded or accompanied by a sensory warning signs called a (aura), such as flashes of light, blind spots, smell or tingling in your arm or leg. A migraine headache then can follow with signs and symptoms, such as nausea, vomiting and sensitivity to light and sound. Migraine pain is usually throbbing and can last for hours or even days.

Inflammatory markers go up rapidly in an attack of Migraines, CRP is elevated, the spinal fluid protein becomes elevated and more white cells are seen in the spinal fluid during a migraine attack. Migraine and epileptic seizure disorders are interrelated and like other autoimmune diseases migraines happen more in women. We have already associated epilepsy with autoimmune-inflammation and so is migraine. Migraine has been treated with anti-inflammatory medication, refractory individuals with migraine respond to prednisone. Migraine often comes in remissions and relapses just like autoimmune disease. Migraine is associated with women just like autoimmune disorders. Some women with Takayasu-disease “pulseless disease” and Lupus present with migraine, as their first symptom. Following anti-inflammatory treatment their migraine attacks usually resolve. Many individuals with lupus present with migraines secondary to severe vasospasm. These individuals have anti-phospholipids antibodies and at times the migraine will only respond to steroids or cyclophosphamide. MRI scans obtained during a migraine have shown dramatic thickening of brain folds called (gyral) with enhancement which suggests

inflammation. In individuals who do not respond to usual migraine treatment one needs to look for inflammation as a cause.

**General symptoms:**

- Throbbing head pain which worsens with physical movement, usually one-sided
- Nausea, Vomiting
- Twisted shining lines in front of the eye sometimes without a headache.
- Weakness or numbness in a hand or leg
- **Sensitivity to light** (Photosensitive headaches respond to magnesium)
- Sensitivity to sound and smell

**Tests:** CRP or E.S.R. can be elevated. Magnesium levels, B6, B1, B12, Folic acid levels. Anti nuclear antibodies and antiphospholipid antibodies are checked to look for lupus.

**Treatment:**

- Prednisone 100mg I/V is given in severe cases, oral treatment from 40 mg a day can be started and tapered over two weeks. In resistant case methylprednisolone and cyclophosphamide pulses are used.
- **Take magnesium supplements total of 400 mg twice a day, and one vitamin B-complex sub lingual formula, to reduce inflammation.** (Increase in extra cellular magnesium concentration, decreases inflammatory response while reduction in the extra cellular magnesium results in cell activation. Because magnesium acts as a natural calcium antagonist, the molecular basis for inflammatory response is probably the result of modulation of intracellular calcium concentration.)
- If the migraine is related to sleep cycles or photophobia add **Melatonin** at 6mg 30 minutes before bedtime daily to help stop the pain cycle. Pain may reoccur on stopping the medicine.
- All the individuals need to be on one **asprin** tablet a day helps control thrombosis associated with anticardiolipin syndrome. In difficult individuals coumadine or heparin can be used and both of these will control the headaches also.
- In cluster headache individuals one cc of lidocaine placed in the nose on cotton wool will stop the headache. Oxygen inhalations will also stop an attack.
- We have only addressed the issue of a Migraine which is immune mediated. For regular migraine use propranolol, timolol, amitriptyline (avoid in autoimmune individuals), sodium valproate, and lisinopril, atenolol, metoprolol, nadolol, fluoxetine, magnesium, vitamin B2 (riboflavin), coenzyme Q10, and hormone therapy in migraine prevention.
- Colostrum supplement used twice daily is useful in migraines.

**Autoimmune Cluster Headache:** Cluster headache is usually seen in men from ages 20-50. The headache tends to occur usually at the same time of the day/night as it is tied to the biological clock. The biological clock is a pacemaking mechanism in mammalian brain that controls circadian rhythms (from the Latin *circa diem*, about 1 day), which are endogenous daily cycles. Dampening of secretory circadian rhythms has been shown for melatonin, cortisol, testosterone, endorphin, and prolactin during bouts of cluster headaches; most of these rhythms revert to normal during remissions.

The headache happens in a cluster of days with pain free interval lasting months. These headaches are associated with autoimmune diseases and anticardiolipin antibodies have been found in these individuals.

**Symptoms of Cluster:** Swelling of the eye, redness, sweating on one side of the face, nasal stuffiness and severe pain the eye or head, usually lasts a few hours. Pain occurs in a cluster of days, happening every day at the same time.

**Tests for Cluster:** antiphospholipid antibodies can be present, E.S.R. can be elevated.

**Treatment of Cluster headache:** Is the same as migraine headaches described above.

**Autoimmune Disc Herniation (ADH) & Sciatica:** Spinal discs are located between each of the vertebrae, which are the interlocking bones in the spine that are stacked on top of each other. The discs act as shock absorbers for the spine and allow it to flex, bend, and twist. There are many different terms used to describe spinal disc pathology and associated pain, such as “herniated disc”, “pinched nerve”, or “bulging disc”. These conditions have been reported to result from autoimmune sciatica (AS). The presence of glycosphingolipid antibodies in individuals with sciatica and disc herniation suggests an activation of the immune system; and suggests a inflammatory process as the cause of sciatica. Usually injuries are associated with herniation, however in recent studies individuals developed back and neck problems without any injury. Individuals had multiple disc lesions, associated with spondylodiscitis (inflammation in disc space). None of these cases had a history of even a minor trauma. Prognosis was good with conservative treatment including NSAID (nonsteroidal anti-inflammatory medications, example asprin), rest, and physical therapy. A biopsy suggested sterile inflammation as the main etiologic factor.

Increased levels of circulating antibodies against one or more glycosphingolipids were detected in 70% of individuals with acute sciatica. In 50% of the individuals undergoing discectomy glycosphingolipids antibodies were seen. During a new attack of pain in sciatica individuals, positive neurologic findings were associated with increased levels of these antibodies.

In another study of individuals suffering from herniation-induced sciatica, a single infusion of 3 mg/kg of infliximab resolved all symptoms for over a 1-year follow-up period. Furthermore, infliximab does not seem to interfere with the spontaneous resorption of disc herniations.

**Symptoms of ADH :** Back pain going down the leg or neck pain going down the arm without history of any trauma, numbness and weakness in the extremity. Coughing and sneezing aggravates the symptoms. Pain may be reduced while lying down in the bed. Some people may have difficulty in controlling their urine.

**Tests for ADH:** MRI scan of the neck/back will show disc herniation, E.S.R. can be elevated, anti-glycosphingolipid autoantibodies (anti-GM1) may be present. Infection is ruled out as a cause by blood tests.

**Treatment of ADH:** All of the autoimmune diseases are remitting and relapsing, individuals who have other autoimmune diseases if they develop back pain, then autoimmune sciatica is the cause of the pain. Treatment should be conservative in all cases of autoimmune sciatica without any need for surgery. Anti-inflammatory drugs can be used including aspirin. High dose pulse steroids, NSAID or other immunomodulatory drugs can be used. Intramuscular 100 mg of steroids are also helpful and can be slowly tapered over two weeks. Please see the list of drugs under the CIDP treatment section. Back surgery can be avoided in these individuals and disc swelling will resolve completely with time.

**Narcolepsy:** Narcolepsy is neurological disorder characterized by excessive daytime sleepiness. It is caused by the progressive loss of protein called hypocretin present in the brain neurons. Hypocretin neuronal cell bodies are located exclusively in the lateral hypothalamus, hypocretin peptides called orexin A and B appear to affect feeding behavior and energy expenditure, arousal, autonomic outflow, which besides regulating body weight also controls water balance, body temperature and a variety of neuroendocrine pituitary functions. An autoimmune process targets hypocretin neurons in response to yet unknown environmental factor. Narcolepsy consists of three main symptoms:

- **Cataplexy** (laughter, anger causing the person to collapse),
- **Hypnagogic hallucinations** (vivid hallucinations during sleeping or awakening),
- **Sleep paralysis** (person wakes up from sleep but cannot move any muscles).

**Cataplexy** is the loss of skeletal muscle tone without any loss of consciousness. The cataplectic attacks are triggered by laughter; embarrassment, anger, athletic exertion or sexual intercourse. During the attack the body becomes limp but the person is awake.

**Sleep paralysis** is an inability to move when falling asleep or awakening. Normal individuals experience sleep paralysis in the second decade of life for a few times. Sleep paralysis is a daily occurrence for narcoleptics. Hypnagogic hallucinations are dreamlike experiences while the person is awake. Examples are a individual saw an airplane land in the middle of a desert, another one saw a bus accident while driving when he stopped his car the road was all clear.

Another symptom of narcolepsy is persistent daytime sleepiness. The narcoleptics fall asleep at inappropriate times, such as driving or flying a plane. Untreated, they are at high risk for motor vehicle accidents and often have trouble at school and the workplace.

**Test for narcolepsy:** The disease is tested by a sleep test called (MSLT) Multiple sleep latency tests. The test measure how long a person takes to enter the dream stages of sleep called REM-sleep. Narcolepsy individuals show a short latency to reach REM sleep. REM means **Rapid Eye Movements** which occur while dreaming.

**Treatment for narcolepsy:** Treatments include stimulants for reducing daytime sleep, with the recent widespread use of modafinil, antidepressants are used for cataplexy, and gamma-hydroxybutyrate for both symptoms. Recently intravenous immunoglobulins

appear an effective treatment of cataplexy if applied at early stages of narcolepsy. Prednisone is also effective in treating all the symptoms of narcolepsy. Finally, the discovery of hypocretin deficiency can be addressed with appropriate supplements in the future.

**Central Pontine Myelinolysis:** Central pontine myelinolysis (CPM) is a disease affecting the stalk of the brain called Pons. All the neural impulses coming from both sides of the brain to move the legs, arms and body pass through the Pons. In CPM the myelin covering in the pons is destroyed, often associated with demyelination of other areas of the brain. Sometimes the term 'osmotic demyelination syndrome' is used for pontine and extrapontine myelinolysis. CPM is seen in post transplant cases and autoimmune disorders like SLE and Sjogrens. Chronic alcoholism is still a common underlying condition of CPM individuals, one case report shows complete reversal of CPM after avoiding alcohol.. CPM following the rapid correction of serum hyponatremia (low sodium) has been common. CPM is also seen in liver transplant individuals where the development of CPM is wrongly attributed to the immunosuppressive agent cyclosporine. CPM has been reported in porphyria.

**Symptoms of CPM:** Paralysis in all extremities is usually seen. Also termed man in barrel syndrome as the arms and legs are paralyzed, the person can only move their eyes. They also have head and neck weakness, dysphagia (difficulty swallowing), and dysarthria.(slurred speech).. Sensation is usually intact.

**Treatment of CPM:** Two cases have been reported where IVIg use led to improvement. In other cases use of steroids has helped reverse the disease.

**Autoimmune Stroke & Transient Ischemic Attacks (TIA):** The American Heart Association and the Centers for Disease Control and Prevention recently published a joint scientific statement about using inflammatory markers in clinical and public health practice. This statement was developed after systematically reviewing the evidence of association between inflammatory markers (mainly CRP) and coronary heart disease and stroke. Both of these organizations have also admitted to an association between infections and inflammation. Infections have long been recognized as a cause of vascular brain disease. Currently, with the growing recognition of the importance of inflammation in atherosclerosis, there has been renewed interest in the possibility that common infections may participate in the atherosclerotic process or lead to stroke through autoimmune mechanisms. Specific organisms that have been implicated include Chlamydia pneumoniae, herpes viruses, human immunodeficiency virus, and Helicobacter pylori. **FHAT** trial showed an association of *h pylori* infection with ischemic stroke.

Commonly individuals are seen who have no risk factors such as smoking, hypertension or high cholesterol yet they have ischemic brain disease. The Northern Manhattan Stroke Study "N.M.S.S." showed an association between C pneumoniae and first stroke in multi-ethnic population. Ischemic inflammatory stroke is commonly seen in younger individuals.

The inflammation can easily be measured by doing a CRP test. Antibodies *C pneumoniae* IgG and IgA were measured in the N.M.S.S. study, they found elevated IgA antibodies to *C- pneumoniae* after the stroke. Another study done in London reported 80 individuals of their stroke individuals were positive for M. Pneumonia antibodies to IgA. This makes it very simple to stop a stroke before it happens. We need to evaluate these individuals for C pneumonia anti IgA antibodies and treat them with Minocin.

#### Tests for stroke risk:

- Screening with IgA and IgG antibodies against *C pneumoniae*.
- Test all individuals either with **E.S.R.** or **CRP** test to see if they are elevated.
- Plasma homocysteine levels to see if they are elevated.

**Treatment to target the source of inflammation in cholesterol:** If CRP, E.S.R. and IgA antibodies against *C pneumoniae* are elevated antibiotic should be used to lower the CRP value.

- If *H. pylori* antibodies are found in the individual then this triple combination should be used. **Azithromycin** (500 mg once daily), **metronidazole** (400 mg twice daily), and **Amoxicillin** (500 mg twice daily) for two weeks. Along with a lacto vegetarian diet, high fluid intake with milk, green tea and water, reduced carbohydrates are recommended.
- For the long term use Fish oil up to 1 gram daily with an **Aspirin** daily by all individuals unless there are contraindications like stomach ulcers or bleeding disorders which can get worse by using Aspirin.
- If homocysteine levels are elevated then treat with vitamin B12, B6 and Folic acid supplements taken sublingually.
- Please follow the diet guidelines in the diet chapter to keep inflammation under control.

**Chapter 7 Cardiovascular Autoimmune Diseases:** Evidence suggests that the leading cause of death in the world is to some degree is infections and that common antibiotics may help bring it under control. In the following section we have not described celiac disease myocarditis, which accounts for less than 2% of the reported cases. However it is a treatable condition and anti-gliadin antibodies can be checked in individuals who are unresponsive to conventional treatments. These patients will respond to dietary management and short term steroids, diet guidelines are provided in the Celiac disease section.

**Kawasaki** disease is an autoimmune disease affecting children. Kawasaki and acute rheumatic fever are the two leading causes of acquired heart disease in children. Rarely adults will be affected. Reoccurrence can happen in later life. Children with Kawasaki disease are between the ages of 5-8 Majority of the individuals affected are of Asian descent. But it can occur in every racial and ethnic group. Over 4,000 cases of Kawasaki disease are being diagnosed annually in the United States. Less



than 1 percent of those who get it will die. *Yersinia pseudotuberculosis* infection has been reported in many individuals with Kawasaki from Japan, which is easily treatable.

*Yersinia-p* is a Gram-negative coccobacillus and a primary pathogen of wild and domestic animals and birds in the tropics. In the human, *Yersinia-p* causes varying degrees of illnesses from diarrhea and abdominal pain to fever, red coloured (scarlatiniform) skin rash, red inflamed eye (conjunctivitis), red bumps on the shin (erythema nodosum), and swelling of lymph nodes (lymphadenopathy). The clinical findings described above are similar to Kawasaki disease presentation. *Yersinia-p* triggered reactive arthritis, eye inflammation, coronary aneurysms, and acute renal failure are an autoimmune response. **Treatment** with ampicillin and tetracycline is usually effective if stool cultures are positive for the infection. This infection is generally seen in Japan among children exposed to non treated water. The antibiotic will not help the arthritis or Vasculitis for which immunomodulatory treatments are recommended.

The **symptoms** of Kawasaki disease are,

- Fever
- Red Rash all over the body
- Peeling skin and swollen red hands and feet
- Red Eyes
- swollen lymph glands in the neck
- Inflammation of the mouth, lips and throat

The coronary arteries are often involved. Part of a coronary wall can be weakened and bulge forming a aneurysm. A blood clot can form in this weakened area and block the artery, sometimes leading to a heart attack. Usually all the heart problems go away in five or six weeks, and there's no lasting damage with treatment. Sometimes coronary artery damage persists.

**Diagnosis** is made by elevated CRP and sedimentation rate with classic clinical findings. *Yersinia pseudotuberculosis* antibodies can be tested in the serum.

**Treatment:** IVIG is the gold standard, if not available steroids 1mg/kg daily and aspirin combination is used. .

- IVIG (intravenous gamma globulin), can decrease the risk of developing coronary artery abnormalities when given early in the illness. The IVIg dose of 2g/kg is given as a single infusion.
- Cases not responding to IVIg, get prednisone, aspirin and IVIg a second time.
- Several studies have shown successful treatment with high dose aspirin and prednisone. Aspirin is used to reduce fever, rash, joint inflammation and pain, and to prevent blood clots from forming.

**Autoimmune Myocarditis: Introduction to autoimmune Myocarditis:** Heart failure is caused by Cardiomyopathy (enlargement of the heart). The heart walls (muscles) become big and large in size which may cause difficulty in pumping blood. Reduced

pumping resulting is difficulty breathing, congestion within lungs and swelling of the feet. The cause of cardiomyopathy is usually a viral infection caused by C.M.V. (Cytomegalovirus). These individuals have been treated with cardiac transplantation. Transplant costs anywhere from one to four million dollars. Individuals generally do not improve after a cardiac transplant and most die within the first year of the transplant. Survivors of transplants develop autoimmune diseases which go unrecognized, have immunodeficiency and cancers. In the last ten years multiple studies have been done which have shown that cardiac transplants can be avoided the individuals can easily be treated simply with IVIG. In one study ten individuals were treated with IVIG who had end stage cardiac failure. One individual died before the completion of the study but nine others walked out of the hospital after completing their IVIG treatment. One year after the treatment they were still doing well. In another study done in Japan nine individuals suffering from Cardiomyopathy were treated with IVIG at a dose of 2g/kg. All of them improved and were doing well even four years after the treatment was given. C reactive protein a marker for inflammation was measured before and after IVIG treatment. It went down considerably with treatment. IVIG seems to be a promising agent in the therapy of acute inflammatory cardiomyopathy.

Lymes disease which results from exposure to *Borrelia burgdorferi* has caused dilated cardiomyopathy which promptly resolved after antibiotic treatment. Serological tests for Lyme Borreliosis have been shown positive in 26% of Cardiomyopathy individuals. Most of the symptoms and heart disease have disappeared after high-dose penicillin therapy.

**A-Rheumatic Autoimmune Myocarditis:** Acute onset of Myocarditis may be seen in any autoimmune disease. Rheumatic fever individuals usually present after dental or tonsillar surgery, with shortness of breath, swelling of joints and elevated anti-streptolysin titer (ASO). The cardiac enzymes are elevated and ECG is abnormal. The cardiomyopathy responds promptly to intravenous antibiotics.

An interesting case reported of a 38 year old ICU nurse who presented with acute myopericarditis, mimicking a new heart attack, confirmed by E.C.G. alterations and elevated cardiac enzymes, group A beta-hemolytic streptococcal tonsillitis was noted. After receiving oral penicillin, the clinical recovery was complete, fever, chest discomfort resolved within a few days of treatment. Furthermore, enzyme levels and C-reactive protein returned to normal within eight days.

Rheumatic fever affects the heart, it usually involves the endocardium, myocardium, and pericardium to varying degrees. Rheumatic myocarditis does not cause any severe valvular damage in the initial attacks, in chronic untreated disease severe mitral valve and aortic valve failure with regurgitation (blood leaking from insufficient valve closure) may be seen. The main cause of cardiac failure is left ventricular dysfunction resulting from myocarditis in

rheumatic fever. Aschoff-nodules are cells seen under the microscope which are a hallmark of rheumatic fever, and have been seen in left side of the heart chambers.

**Symptoms:** Tiredness, shortness of breath, fatigue, coughing and blue discoloration of skin.

**Tests:**

- Blood test for ASO titer which is elevated,
- Echocardiogram of the heart to check the valves and the left heart chamber for damage.
- CRP is elevated

**Treatment:**

- Penicillin (either oral penicillin V or injectable Benzathine penicillin) remains the treatment of choice, because it is cost effective, has a narrow spectrum of activity, has long-standing proven efficacy.
- Macrolides (clindamycin), oral cephalosporins (cefixime),
- Oral amoxicillin is mainly used for penicillin-allergic individuals; alternatives are clindamycin, azithromycin, or Clarithromycin.

Individuals with autoimmune diseases need antibiotics before they have dental or medical procedures. These are as follows.

- Prosthetic cardiac valves, Previous bacterial endocarditis
- Complex cyanotic congenital heart disease
- Surgically constructed systemic-pulmonary shunts or conduits
- Congenital cardiac defects
- Acquired valvular dysfunction (eg, rheumatic heart disease)
- Hypertrophic cardiomyopathy
- Mitral valve prolapse with valvular regurgitation and/or thickened leaflets

**B- Chronic Lyme Myocarditis** is the least well documented complication of Lyme disease. Cardiac involvement usually occurs within weeks of the infecting tick bite and includes varying degrees of atrioventricular block (impaired electrical activity in the heart) as the commonest manifestation and tachyarrhythmia's (fast heartbeat), myopericarditis (heart muscle dysfunction). There has been evidence that cardiomyopathy is associated with long term *Borrelia burgdorferi* infection. Individuals with **atrioventricular block** have good prognosis and this is the leading presentation in Lyme's Carditis. **Progressive arrhythmia** (irregular heartbeat) and heart failure combined with neurological symptoms

that can be resistant to conventional cardiological treatment (**individuals don't respond to medications**). Most cases confirmed by positive antibodies to Borrelia.

**These findings are an indication for antibiotic treatment.** Transient atrioventricular block (AV) is the most frequent manifestation of Lyme carditis, sometimes there is complete AV block which means that electrical impulses from the small chambers do not proceed to the big chambers of the heart.

**Symptoms:**

- Shortness of breath with activity (exertional dyspnea).
- Rapid heart beats (palpitations).
- Dizziness and tendency to lose consciousness (syncope).
- There may be repeated attacks of passing out spells with irregular heart beats.

**Test:**

- Blood test is done to check for Lyme antibodies.
- EKG will show cardiac conduction defects like irregular rhythm, blocked AV conduction.

**Treatment: There is no need to place permanent pacemakers for Lyme carditis.**

- Antibiotic treatment with intravenous doxycycline results in complete remission of all cardiological symptoms. Oral treatment should be continued for six months 200 mg on alternate days three times a week is prescribed.
- According to the severity of the disorder, antibiotics are administered orally (penicillin or derivatives) or parenterally with penicillin or cephalosporin's of the 3rd generation over 4 and 2 weeks, respectively. Standard antibiotic treatment with intravenous Ceftriaxone 2 g bid for 14 days.
- Fish oil up to 1 gram daily with an Asprin should be used by all individuals unless there are contraindications like stomach ulcers or bleeding disorders which can get worse by using Asprin.

**C-Autoimmune Viral Myocarditis** (Human Parvovirus B19, Varicella Zoster, Coxsackie, Influenza A, Hepatitis C and Epstein-Barr virus): Viral Myocarditis can occur in children or adults usually causes chest pain and fever, with heart failure. There is recent history of viral illness and no past history of cardiac failure.

**Influenza Myocarditis history:** Influenza A virus is well known for its capability for genetic changes. As we trace backwards through the history of influenza pandemics, a repeating pattern can be observed, a limited wave of infections in the first year followed by global spread in the following year. In the 20th century alone, there were three overwhelming pandemics, in 1918, 1957 and 1968. High mortality was seen in infants,

elderly and sick. In 1918, there was one distinct peak of excess death in young adults aged between 20 and 40 years old. Autopsies show multiple-organ involvement, including pericarditis, Myocarditis, hepatitis and splenomegaly. Influenza Myocarditis appears autoimmune due to multi organ involvement. Influenza will strike again we need to be prepared to stop autoimmune reactions. The answer will be nanoparticles.

#### **Tests for Viral Myocarditis:**

- ECG shows elevation of the S & T waves suggesting a heart attack pattern.
- Creatine kinase (CPK) is elevated suggesting heart attack or varicella infection.
- The left side of the heart is enlarged and left ventricular ejection fraction is globally reduced (ejection fraction 45%).
- Myocarditis is confirmed by a biopsy showing lymphocytic myocarditis.

#### **Treatment**

- Acyclovir, or Valacyclovir 1 gram three times daily as an antiviral
- Prednisone and azathioprine for 6 months for immunosuppression.
- Non-steroidal anti-inflammatory drug like aspirin used daily. During one to two months the individual recovery is usually complete.
- IVIg, or varicella hyperimmunoglobulins
- Early treatment can avoid a transplant.

**D-Giant cell Myocarditis (GCM) the most fatal Disease:** GCM is a rare, frequently fatal inflammatory disorder of cardiac muscle. It occurs in children, teenagers and adults. In some people it develops after flu like illness. There is an association of Myasthenia gravis and malignant thymoma developing after individuals are placed on immunosuppressive treatment, or after thymoma surgery. Rarely SLE individuals may develop GCM in the course of their treatment. Majority of the people getting this disease are healthy. There has been a high mortality reported in this disorder of 90% with and without heart transplant. It can reoccur in transplanted heart tissue. IVIg treatments have not been reported in this disease. Double vision with orbital Myositis can be an early presentation with GCM.

#### **Symptoms:**

- Most present with shortness of breath,
- Irregular heart beats, chest pain.
- Eye may swell up and bulge due to Myositis a week before the heart gets involved.

**Test:** Erythrocyte sedimentation rate usually 100-108 mm/h at the first hour. C-reactive protein elevated 150 mg/L (normal value, < 5 mg/L. In early stages the Cardiac ECHO, and angiogram can be normal. The tests can rapidly become abnormal within a day. The biopsy will show classic inflammation and giant cells (extensive inflammatory infiltrates mainly represented by lymphocytes, histiocytes, eosinophils, and multinucleated giant cells).

**Treatment:**

- Below is the protocol, which was successfully used in a individual who survived.
- The individual received IV prednisolone, 7 mg/kg for 3 days, followed by 1.5 mg/kg/d orally for 2 weeks. This was later reduced to 1 mg/kg/d for 4 weeks. Then prednisone was reduced to 0.33 mg/kg/d and azathioprine, 2 mg/kg/d was started. After 6 months, steroids were tapered and withdrawn. Azathioprine from the sixth month was reduced to 1 mg/kg/d. At 16 months of follow-up, the individual is receiving maintenance low doses of azathioprine, and is still asymptomatic with normal cardiac volumes and function
- In conclusion, conventional doses of steroids and azathioprine may relieve in some cases the severe cardiac compromise of a giant cell myocarditis, avoiding the need for heart transplantation.
- Two cases have been reported one of a teenage girl and a boy who developed GCM while on IVIg treatment for Guillian Barre Syndrome. Both cases responded to azathioprine and steroids.

**Autoimmune Myocarditis in Athletes-There is an increased incidence of deaths in athletes due to Myocarditis:** The athlete represents the healthiest segment of our society. Yet, there are still reports of sudden death occurring while on the athletic field. Any athlete who 'goes to ground' temporarily (syncope), should be treated for myocarditis. Myocarditis should be suspected in athletes with unexplained cardiac arrhythmias and dysfunction, especially if preceded by a flu-like syndrome. An early diagnosis is desirable in order to avoid the risk of fatal consequences, since physical activity can enhance the inflammatory process. In the presence of life-threatening arrhythmias or rapidly progressive cardiac dysfunction an antiviral or an immunosuppressive treatment should be considered depending on whether a viral agent is present or absent, respectively, in the myocardium.

**Symptoms:**

- Some athletes are free of symptoms,
- Some complained of nausea and vomiting, vertigo, weakness, epigastria pain.
- Shortness of breath (dyspnea),
- Chest pain with activity (angina pectoris symptoms), nausea.

- Backache and palpitation.

#### **Tests:**

- Cardiac enzymes and an elevated.
- ESR and CRP are elevated.
- ECG, stress ECG, echocardiography and stress-echocardiography are abnormal.
- Although several diagnostic tools can be useful for the diagnosis of myocarditis, endomyocardial biopsy is still the gold standard

#### **Treatment:**

- Athletes recovering from acute myocarditis should abstain from moderate exercise. Rest is the most effective strategies in myocarditis management. Athletes need to be on a normal fat diet. Good hydration and use fish oil as an anti inflammatory.
- Physical exercise is contraindicated in acute respiratory infection. Athletes with myocarditis should be withdrawn from all competitive sports for at least 6 months and resume training when ventricular function and cardiac dimensions return to normal and the clinically relevant arrhythmias disappear.
- Preventive medical examinations are essential, especially in athletes before physical exercise, as are other investigations in every case suspicious of heart disease, including electrocardiogram (ECG), stress ECG, echocardiography and stress-echocardiography.

**Autoimmune Atherosclerosis:** April 15, 2005 issue of Clinical Infectious Diseases, a study reported showing a link between Chlamydia pneumoniae and Heart Attacks in young people. Researchers in Wisconsin and Maryland conducted a study of young men in the military to determine whether there was a link between C. pneumoniae infection and heart attack, also called myocardial infarction. They examined the blood of 600 men: 300 men between 30 and 50 years old who had been hospitalized for a previous heart attack, and 300 matched controls. Because the subjects were in the military, the researchers could examine blood samples that were collected and stored in the Department of Defense's serum repository before the men had their heart attacks. They found that high levels of C. pneumoniae antibodies in blood were associated with the occurrence of heart attack. This association was particularly strong in blood collected one to five years before the men's first heart attacks.

Accumulating evidence supports an autoimmune mechanism as one of the prime pathogenic processes involved in the development of atherosclerosis and heart attack.

About 50% of people having myocardial infarction (MI) or strokes are not exposed to any of the risk factors like lipids and smoking. Yet they go on to develop arteriosclerosis. In autoimmune diseases, such as systemic lupus erythematosus (SLE), Antiphospholipid syndrome (APS), rheumatoid arthritis and Vasculitis, one can also find progression of arteriosclerosis, suggesting that inflammatory and autoimmune mechanisms are involved in the process of plaque formation. Many viruses, bacteria and even parasites are claimed to affect AS plaque deposition. Among them, *Chlamydia pneumoniae* probably has the strongest association with.

Recently several viruses, including herpes simplex, cytomegalovirus, and coxsackie B virus, have been implicated in heart disease. ***Chlamydia pneumoniae*** is among the new emerging infections which have been linked to atherosclerosis.

*Chlamydia pneumoniae* usually causes respiratory conditions that can progress to pneumonia. Chances are most of us are already carrying this bug. Anti *Chlamydia* antibodies are found in people all over the world. *Chlamydia pneumoniae* makes its way into the walls of various blood vessels, where it induces the inflammation and immune reaction that causes heart attacks and strokes.

Seroepidemiologic studies have associated *C. pneumoniae* antibody with coronary artery disease, myocardial infarction, carotid artery disease, and cerebrovascular disease. The association of *C. pneumoniae* with atherosclerosis is corroborated by the presence of the organism in atherosclerotic lesions throughout the arterial tree and the near absence of the organism in healthy arterial tissue. *C. pneumoniae* has also been isolated from coronary and carotid atheromatous plaques.

American heart Association and Centers for Disease Control have issued joint statements stating that low level inflammation caused by, ***Chlamydia pneumoniae***, ***Helicobacter pylori***, are possible causes of heart disease and stroke. There are more than two hundred reported studies showing the relationship of *C. pneumoniae* to Atherosclerosis. Many studies tried treating these individuals with a single antibiotic, some succeeded but majority did not. The answer is simple; we need a combination of antibiotics as there are multiple microorganisms involved, this was successfully done in the study reported below.

For treatment of Cardiac problems, autoimmune arteriosclerosis it is recommended that Doxycycline and tetracycline, erythromycin or ciprofloxacin be used, in individuals who have elevated CRP or those who are positive for *Chlamydia* antibodies.

In a (randomized) study, 88 heart individuals were treated with azithromycin 500 mg per day for 2 days after that the dose was reduced to 250 mg per day for 28 days. After 6 months, those individuals receiving azithromycin had lower frequencies of both angiographically confirmed restenosis and recurrent angina than individuals receiving placebo, (Circulation 1998; 97:1669-70).



In another large study which looked at infections with *Helicobacter pylori* and *Chlamydia pneumoniae*, in associated with coronary heart disease. This study was named the South Thames trial of Antibiotics in Myocardial Infarction and unstable Angina (STAMINA). There were three groups in this study, and two groups on multiple antibiotic combinations. Within twelve weeks of starting antibiotic treatment C-reactive protein levels were reduced, with 36% reduction in death and Myocardial Infarction was noted. This reduction in inflammation persisted during the first year of follow up in the antibiotic treated group. Neither *C. pneumoniae* nor *H. pylori* antibody status was related with response in treatment. Antibiotic treatment significantly reduced adverse cardiac events in individuals with acute coronary syndromes, but the effect was independent of *H. pylori* or *C. pneumoniae* seropositivity. The antibiotic combination used were **amoxicillin** (500 mg twice daily), **metronidazole** (400 mg twice daily), and **omeprazole** (20 mg twice daily). Second group used **azithromycin** (500 mg once daily), **metronidazole** (400 mg twice daily), and **omeprazole** (20 mg twice daily). (Circulation. 2002 Sep 3;106(10):1219-23. Stone AF)

The STAMINA study shows two important observations, the *H. pylori* & *C. pneumoniae* antibodies were associated with inflammation, within the blood vessels which responded to antibiotics with reduced Cardiac events in antibiotic treated individuals. The antibody levels against bacteria did not change which makes one wonder if long term antibiotic treatment is needed. Intravenous immunoglobulin (IVIg) therapy leads to a 40% reduction in the extent of plaque formation. It is likely that IVIg acts in part through anti-idiotypic antibodies. The role played by IVIg confirms the issue that with any antibiotic treatment we need to combine an anti-inflammatory treatment.

Many other studies looking at causes of inflammatory heart disease have also found a relationship between elevated homocysteine levels and heart disease.

**Conclusion:** A causative role of *C. pneumoniae* infection in cardiovascular disease has been observed. The high frequency of infection found in human atherosclerotic tissue in comparison to normal tissue, the induction and progression of atherosclerotic like inflammation and the early results from antichlamydial intervention studies in humans are consistent with a causative role of *C. pneumoniae* in the disease process.

#### **Testing for autoimmune atherosclerosis:**

- **Check the CRP (if it is high then use an antibiotic).**
- **Antibodies to *C. pneumoniae* & *H. pylori***
- **Check homocysteine levels (to see if elevated)**

#### **Treatment to target the source of inflammation in cholesterol:**

- If the individual has elevated CRP then they need to be given **azithromycin** (500 mg once daily), **metronidazole** (400 mg twice daily), and **omeprazole** (20 mg twice daily) for two weeks.

- If homocysteine levels are elevated then treat with vitamin B12, B6 and Folic acid supplements.
- Fish oil up to 1 gram daily with an Asprin should be taken by all individuals unless there are contraindications like stomach ulcers or bleeding disorders which can get worse by using Aspirin. CRP levels have been brought down by Fish Oil.

Do not wait to become a statistic, get your CRP checked.

**Chapter 8 Ophthalmic Autoimmune Diseases:** The eye is often compared to a camera. Light comes in through the cornea, pupil, and lens at the front of the eye just as the lens of the camera lets in light to the film. The light is then focused on the inside wall of the eye called the retina (as on the film in a camera). This picture is then sent to the brain along the optic nerve which connects the eye to the brain. When the eye turns red it is the result of inflammation. Even a bacterial or viral infection is accompanied by inflammation. Ocular inflammation may affect all eye layers, conjunctiva, sclera, and uvea. If we think of the eye as a multi layered ball, then the outer layer is the sclera a protective layer, the innermost is the retina the thin light gathering layer (eyes video screen), and the middle layer is the Uvea. The Uvea is made up of the iris (the aperture), the Ciliary body and the choroid. When any part of the uvea becomes inflamed then it is called Uveitis.

#### **Autoimmune eye diseases:**

- **Iritis**, Is the inflammation of the iris also called **anterior** uveitis. This condition is often associated with autoimmune disorders such as arthritis.
- **Uveitis** is inflammation of the **middle portion of the eye** and may affect the muscle that focuses the lens. This also may develop suddenly and last several months.
- **Retinitis** affects the **back of the eye**. It may be rapidly progressive, making it difficult to treat.
- **Choroiditis**, or inflammation of the layer beneath the retina,

Iritis, retinitis, choroiditis and uveitis can all be caused by autoimmune diseases. The autoimmune process can be triggered by injury to the eye. Many systemic diseases cause diffuse inflammation by an autoimmune mechanism. These include tuberculosis, spirochaetal diseases such as Lyme disease and syphilis, sarcoidosis, Behcet syndrome, juvenile idiopathic arthritis, and HIV infection. Their role in autoimmune disease should always be suspected. Confirming the diseases by appropriate test will help direct the correct combination of antibiotic and anti inflammatory treatment.

The uveal tract represents the vascular organ of the eye. In addition to providing most of the blood supply to the intraocular structures, it acts as a conduit for immune cells, particularly lymphocytes, to enter the eye. Consequently, the uveal tract is represented in many intraocular inflammatory processes. Uveitis is probably a misnomer unless antigens

within the uvea are the direct targets of the inflammatory process. A better term of the condition is "intraocular inflammation" (IOI).

In autoimmune diseases with intraocular inflammation (IOI), uveitis may be the first clinical manifestation and may represent the most severe sign. The conventional treatment of IOI includes prednisone and immunosuppressive agents, which are efficient in around half of the individuals; however, their effectiveness is also limited by their side effects. The effects of intravenous immunoglobulin (IVIg) on ocular inflammation have been reported in a number of autoimmune diseases. They show favorable results in ocular cicatricial pemphigoid, ocular pemphigus, Wegener disease, Behcet's disease, inflammatory myositis. IVIg and assess their potential steroid-sparing effect. Whenever Iritis is noticed by a physician it should be a clue to that the individual may be developing autoimmune disease in the future.

**Causes of autoimmune Iritis** ankylosing spondylitis, reactive arthritis (including Reiter's syndrome), psoriatic arthritis, inflammatory bowel disease, **Behcets disease, sarcoidosis**, juvenile chronic arthritis, Vogt-Koyanagi-Harada syndrome (an inflammatory syndrome including uveitis with dermatologic and neurologic manifestations).

**Testing:** Blood tests for total white cells, vitamin B-12 levels, homocysteine level, folic acid level, pyridoxine level and cultures of eye fluids are done. E.S.R. is elevated. ANA, anti-Ro (SS-AA) antibody to check for Sjogrens and antithyroid antibodies to look for thyroid disorders.

### **Current treatment guidelines**

- In an inflammatory disease of the eye there will always be an associated infection. In the autoimmune diseases the inflammation is accompanied by an infection. Thus we recommend a topical antibiotic be used in all inflammatory eye conditions. We recommend Minocin as it has anti-inflammatory properties. It is best to use a prednisone ointment or eye drops with the antibiotic.
- Immunosuppressive drugs we recommend, Steroid eye drops or ointment may be needed. Other anti-inflammatory drugs that are available include Azathioprine, Methotrexate, Mycophenolate Mofetil, Cyclosporine, Tacrolimus, Cyclophosphamide, and Chlorambucil.
- IVIG is very effective in ocular Pemphigoid / Pemphigus and if the treatment is not started early this condition can lead to blindness. The recommended I.V.I.g dose is 2g/kg every two weeks in divided doses

**Double Vision in autoimmune diseases:** If a new individual develops double vision they need to be evaluated for autoimmune diseases such as, Thyroiditis, Myasthenia

Gravis, Eaton Lambert Syndrome, Multiple Sclerosis, Guillain-Barre, Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Lyme and Myositis. Please see treatment guidelines under the specific condition. Infections such as Botulism or Botox injections can also cause double vision. Giant cell Myocarditis individuals present with double vision and Myositis as the first symptom. CRP and E.S.R. should be done on all individuals, any one with CRP over 80 should be started on Intravenous steroids one gram a day.

**Sympathetic Ophthalmia (SO):** This is an autoimmune disease in which a penetrating injury to one eye produces inflammation in the fellow, non-injured eye. Sympathetic ophthalmia was known to Hippocrates over 2000 years ago. This rare reaction can follow a cataract removal procedure, ocular surgery and especially vitreo-retinal laser surgery. The uvea is involved in early stages later the Ciliary body. The release of uveal pigment into the bloodstream is thought to cause antibodies to be produced which initiate uveitis in the fellow eye.

**Symptoms:** Early features are floating spots and weakness of accommodation. The retina is rarely affected but papilloedema and glaucoma may result. Approximately two-thirds of SO cases occur within two weeks to two months following injury, with 90% occurring within the first year. Usually individuals notice blurry vision and pain in both eyes without other symptoms outside the eyes. Eye examination usually shows red and painful eyes with a swollen middle layer of the eye called the uvea.

**Tests:** There are no tests needed for this condition, a diagnosis is based on the history of a injury which happened within a year.

**Treatment:** Early administration of systemic steroids may be helpful. If the injured eye remains inflamed and there is little prospect of it recovering vision, then sympathetic ophthalmia an intravitreal injection of 4 mg of triamcinolone acetonide reduce the likelihood of sympathetic ophthalmia. Action is usually required within two weeks of injury. In Sympathetic ophthalmitis a combination treatment with steroids and antibiotics has been used successfully, Penicillin and azathioprine has been used. Long term remission can be achieved by corticosteroids started at 250 mg BID for two week and then cut down to 125 mg daily as maintenance for 2-3 months.

**Optic Neuritis or Retrobulbar Optic Neuritis – sudden loss of vision:** The optic nerve is an extension of the brain that connects the retina of the eye to the brain. The retina contains photoreceptors, cells that are activated by light and that connect to other retinal cells called ganglion cells. These, in turn, send long information through projections called axons into the brain. By this route, the optic nerve sends visual impulses to the brain. Optic neuritis is the most common optic nerve disease to affect young people. The average age at the first attack is 30 years, but teenagers and people at any age may develop this disease. The intense inflammation in the optic nerve can be seen by the MRI scan and even by looking in the eye.

**Symptoms:** In optic neuritis heat will make the symptoms worse phenomena called Uthoff's phenomenon. On examination there can be swelling of the optic nerve seen when looked inside the eye, the optic disc looks chalky white and with time will look pale. The pupil, located in the center of the iris, is the part of the eye which gets larger and smaller according to the amount of light. The optic nerve plays a role in this reaction to light, in the normal eye the pupil quickly becomes small after a bright light is brought in front of it. If one eye has retinal or optic nerve disorders, then if we shine light on the normal eye that pupil constricts, and then shine the light on the bad eye, instead of constricting the pupil dilates immediately in that eye. That is what is called a relative afferent pupillary defect.

**Test:** ESR is done to check for inflammation, vitamin B-12, B-6 and Thiamine levels to look for vitamin deficiency, Homocysteine levels to look for elevation. Mycoplasma antibodies and Lyme antibodies in blood may be present. MRI scan of the head to look for tumors, strokes and inflammation in the optic nerve. Some people with optic neuritis may have a few Multiple Sclerosis plaques in the brain.

**Treatment:**

- Steroids 1gram loading dose intravenous for three days followed by 100 mg a day prednisone and tapered over a month.
- If homocysteine is elevated give vitamin B-12 replacement with folic acid and pyridoxine.
- If the MRI shows multiple lesions like Multiple Sclerosis then please look in the MS chapter for guidelines on treatment.

**Orbital Myositis & Tolosa-Hunt syndrome or orbital pseudotumor**

**syndrome:** Inflammation and swelling of the muscles around the eye is termed orbital Myositis (Tolosa-Hunt syndrome or orbital pseudotumor). It can be seen in many conditions some examples are, thyroid orbital Myositis, Wegener's granulomatosis and sarcoidosis. This condition should be considered in individuals who have unusual symptoms such as protrusion of the eyeball, painful eye movements, or pain that does not resolve within three hours. Myositis in thyroid myopathy is usually painless in onset, is similar in both eyes, slowly progressive, and associated with systemic manifestations of Graves disease (weight loss, enlargement of thyroid). Rarely individuals may present with double vision and Myositis, who within weeks can die if not treated with steroids as they have G.C.M (Giant Cell Myocarditis)

**Symptoms:** Pain and swelling around the eye are the most common clinical features. In all cases, protrusion of the eyeball, swelling of the eyelid, painful eye movements, reduced or blurred vision are seen. Redness in the eye is seen.

**Symptoms of thyroid myositis:** limitation of the movement opposite to the affected muscle, and deterioration of color vision, visual field, and visual acuity may also occur in thyroid eye disease. These individuals also have weight loss despite increased appetite, nervousness, and palpitations. They can also appear fatigued or drowsy.

**Tests:** E.S.R. is elevated, CRP is elevated and MRI Scan of the orbit should be done which can show swelling of the muscles. A culture of inflamed site for fungal or bacterial infections is usually obtained. Antithyroid antibodies need to be checked and A.N.A is done to screen for Lupus activity. To evaluate for Lyme disease a Borrelia antibody test is

done. Vitamin B-12 levels, Thiamine levels and B-6 levels with homocysteine levels need to be measured.

**Additional tests for Thyroid Myositis:** laboratory testing for thyroid hormones T3 (triiodothyronine), T4 (tetra-iodothyronine) and TSH (thyroid stimulating hormone) are indicated.

#### **Treatment of Orbital Myositis:**

- If CRP is in the 80-100 range hospitalizes the individual and give intravenous steroids at Gram a day for 5 days. If CRP is below 80 then use oral Prednisone is started for a few days at 50 mg daily and tapered down after the swelling becomes less. Methotrexate is used as a corticosteroid sparing agent with antibiotics if necessary based upon clinical observations.
- Those individuals whose clinical or radiological features are associated with inflammation of the muscles will benefit from early systemic steroid therapy. Methotrexate given at a dose 20 mg per week (range 15-25 mg per week) in conjunction with folate supplementation helps control inflammation. Individuals need regular ophthalmic examinations, as well as serum liver enzyme levels and blood cell counts to monitor side effects of Methotrexate.

#### **Treatment for thyroid Myositis:**

- Propylthiouracil (Tapazole) are used to block the synthesis of thyroid hormone, propranolol (Inderal) is also used to slow down the increased metabolism.
- Systemic steroids, immunosuppressive agents like azathioprine, cyclosporin or cyclophosphamide in combination with orbital irradiation are used in advanced cases of Myositis.

## **Chapter 9 Skin & Hair Autoimmune Diseases**

**Autoimmune Urticaria:** Urticaria is usually considered idiopathic in reality the chronic form is autoimmune. The chronic reoccurring Urticaria is like remitting relapsing autoimmune disease. It can be treated with anti-inflammatory medications. Chronic urticaria has been described in individuals with *Helicobacter pylori* infection. Due to this there is a higher prevalence of B-12 deficiency in Urticaria. Positive anti-H.Pylori antibody is found in most individuals with Urticaria and the condition resolves with antibiotic treatment in sixty percent of the individuals. Search for H pylori should be included in the diagnostic management of chronic urticaria. There is an association between thyroid autoimmunity and chronic urticaria. Some individuals who have Thyroiditis have positive antithyroid antibodies. Treatment of the thyroid disorder helps correct the urticaria.

**Symptoms:** Urticaria, commonly known as hives, it consists of circumscribed areas of raised erythema and edema of the superficial dermis. There is swelling, itching, pain and

rash of the skin seen.

**Test:** Antigliadin antibodies, h.pylori antibodies, antithyroid antibodies. Vitamin B12 levels are sometimes low.

**Treatment:**

- For H.pylori eradication began treatment with amoxicillin, clarithromycin and omeprazole for 14 days. About fifty percent of the individuals will recover with above treatments. Those that do not respond need to be placed on levofloxacin (500 mg b.i.d.), amoxicillin (1 g b.i.d.), and omeprazole (20 mg b.i.d.) was prescribed for 10 days. A urea breath test can be done to confirm if the treatment was effective. Above combination is recommended if anti-H.pylori antibodies are present or if a low B-12 level is found. For Low B12 levels take a sublingual B12 formula or intramuscular injections one a month.
- If thyroid antibodies are positive treatment with levothyroxine will help improve thyroid functions and help the urticaria.
- Resistant individuals may need Dapsone 50 mg daily to alleviate the condition. Urticaria individuals, who have high antibody titers, to either herpes simplex virus or Epstein-Barr virus, will respond to Acyclovir 100mg given every six hours. In those with chronic urticaria who do not recover they need treatment with I.V.I.g. The dosage used is 500mg/kg alternate days for four days.
- **Individuals need to go on a MSG free diet if urticaria does not clear up.**

**Alopecia areata:** Hair helps transmit sensory information they grow out of follicles, there are 5 million follicles on the body. One million of those are on the head. Loss of hair is called alopecia it is considered an autoimmune disease, the immune system mistakenly attacks the hair follicles, the tiny structures from which hairs grow. In most cases, hair falls out in small, round patches about the size of a coin. In many cases, the disease causes a few bare patches. In others hair loss is more extensive. Rarely, there is total loss of hair on the head (alopecia areata totalis). Family members may have a history of autoimmune diseases, such as diabetes, rheumatoid arthritis, thyroid disease, systemic lupus erythematosus, or pernicious anemia. Higher occurrence of thyroid disease, atopic eczema, nasal allergies, and asthma may be present in some individuals.

**Symptoms:** Patches of hair falling out.

**Test:** Check for Iron deficiency in all individuals especially during pregnancy. Check for thyroid deficiency (check antithyroid antibodies) and Vitamin B-12 (Cynocobalamine deficiency). Check for antigliadin antibodies. Check for H.Pylori antibodies.

**Treatment:**

- **MINOCIN:** Minocin 100 mg daily should be given to all new cases of alopecia. There is complete resolution of symptoms and hair regrowth is good. It should be continued for two to three months. Best to take the medicine at night with water and no food.
- **Iron Supplements:** In those individuals who have anemia or iron deficiency.
- With baseline serum vitamin B12 **levels below 350 ng/l**, need supplements of Cynocobalamine. (Sublingual formula daily or injections monthly)
- Give Zinc supplements to children with hair loss.
- **Corticosteroids:** Prednisone if there is no response to minocin, 8 mg/kg body weight) intravenously on 3 consecutive days at 4-week intervals for at least 3 courses. Called the pulsed treatment.
- **IVIg & Interferon gamma** (see report below)
- Proscar **finasteride** is effective in male pattern hair loss.
- Melatonin 0.1 % solution applied daily to scalp improves alopecia
- Postmenopausal women need Minoxidil solution to be applied to the scalp
- **PUVA:** Photochemotherapy combining oral or topical methoxsalen and UV-A irradiation of the scalp improves alopecia.
- A woman, with atopic dermatitis and alopecia areata universalis, was treated with systemic interferon gamma, administered subcutaneously, the viral infection cleared and four weeks later hair re-growth was observed. Complete remission of alopecia areata was documented. After four cycles of high-dose 500mg/kg intravenous immunoglobulin, a sustained remission of the atopic dermatitis was achieved.
- In another case a young girl with immune deficiency was treated with IVIG and regrowth of eyelashes, eyebrows, body and scalp hair was observed in this individual. This has been reported several times and thus IVIg should be considered as a treatment for immune deficiency associated with alopecia.
- If low B12 levels are found then treatment with the antibiotic combination described under Urticaria for H.Pylori eradication should be done.
- Many individuals with immune deficiency who had hair loss started to grow their hair after they received I.V.I.g.

**Autoimmune Atopic Dermatitis or Eczema:** Atopic dermatitis (AD) is a chronic, itching, inflammatory skin disease which is associated with asthma or hay fever and a familial occurrence of these conditions. The disease comes in attacks which improve with time, and then there are more attacks. Genetic factors are important in the development of AD. There are a number of different eczemas - which cause the skin to become inflamed and itchy. This condition is also called 'atopic eczema' or 'infantile eczema'. It affects people with dry and rough skin and may be caused by a variety of allergens. It often starts in childhood and tends to run in families. It often progresses to asthma and allergic rhinitis later in life.



Individuals with atopic dermatitis often have elevated serum IgE levels and sensitization against a variety of environmental allergens, but there is also evidence that attacks of the disease occurs in the absence of exposure to environmental allergens. There has been a significant association between the appearance of mite (*Dermatophagoides pteronyssinus*, *D. farinae*)-specific IgE and ACL IgM antibodies reported in atopic dermatitis. Some causes of atopic dermatitis can include:

- Food allergies (Which are more likely to affect children)
- Cow's milk and hen's egg are the foods most likely to make infantile eczema worse.
- The house dust mite -. Allergy to cats and dogs.
- Bacteria such as staphylococci may cause sudden severe outbreaks of eczema.
- Fungi like candida, Malassezia yeasts, House dust mites or food.
- H.pylori infection.

**Tests:** Eosinophils and IgE are elevated, anti-nuclear antibodies and Antiphospholipid antibodies may be present. Antigliadin antibodies may be present. Combined skin prick and patch testing significantly enhances identification of food allergy in children. Especially for foods listed above and Fungi.

**Treating of Eczema:** Eczema triggers, need to be avoided by individuals. Eczema can be treated with low dose steroid ointments. Anti-histamines like benadryl can be used to make the skin less itchy and these should also help at night by reducing itchiness. Those individuals who have Candida improve with antifungal treatments; Fluconazole is more effective than amphotericin B and nystatin, for fungal treatment. Tacrolimus is a topical immunosuppressive ointment without systemic effects. It may be useful in children and adults with severe atopic dermatitis. In resistant cases interferon treatment can be used. We recommend Fish oil as a anti-inflammatory in all people. If the condition does not improve IVIg will usually resolve the dermatitis.

**Vitiligo:** Vitiligo is an autoimmune disease in which pigment producing cells (melanocytes) are destroyed by the immune system. Loss of the pigment cells results in irregularly shaped white patches on the skin. Any area of the body can be affected. Common locations are face, neck, eyes, nostrils, nipples, and genitalia. Reduced pigment is also seen at sites of injury and around moles. The hair is also affected on the scalp, eyebrows, eyelashes and body. When compared with the normal population, individuals with Vitiligo often showed diminished blood levels of folic acid, diminished levels of vitamin B12 serum and low levels of ascorbic acid plasma. The incidence of autoimmune disorders in these individuals and their family members is higher, diabetes mellitus, rheumatoid arthritis and SLE are frequently seen. Many people report that their vitiligo first appeared following a traumatic or stressful event, such as an accident, job loss, death of a family member, severe sunburn, or serious illness. Vitiligo is after reported after interferon treatment.

**Symptoms:** Irregular depigmented spots begin to appear on different parts of the body. Especially after an injury they will develop within the injured area.

**Test: Vitamin levels** of B-12, Folic acid, Thyroid antibodies, antigliadin antibodies for celiac disease.

**Treatment:**

- Individuals will benefit from supplements of vitamin B12, folic acid and fresh fruits taken daily. The vitamin should be a sublingual formula. Individuals need to be advised about sun exposure allowed only in the morning and evening. They should avoid the full afternoon sunshine.
- Combination therapy with **topical vitamin D-(3)** ointment and linear polarized infrared, UVA, solar irradiation, can be used as an alternative therapy for Vitiligo. Those who cannot have access to sunlight can use UVB lamps in winter time.
- Short term steroid creams can be used to help areas of skin if they are itching.
- Topical calcipotriol treatment was applied twice daily as 50 microg/gm cream or ointment is helpful for those individuals who fail the sunlight exposure treatments.
- Narrow band UVB is succeeding psoralen and UVA irradiation as the main treatment of vitiligo vulgaris. UVB combined with vitamin B12 and folic acid has been successful in resistant cases.
- The xenon-chloride excimer laser represents a new treatment modality for the management of stable vitiligo.
- If thyroid antibodies are positive then treatment of thyroid disorder is recommended by levothyroxine. If antigliadin antibodies are positive treat for celiac disease, as described in the celiac disease section.

**Pemphigus vulgaris:** Pemphigus vulgaris is an autoimmune disease that is characterized by blisters and ulcers on the skin and mucous membranes, most commonly inside the mouth. The cells of the epidermis (upper layer of the skin) called keratinocytes, are cemented together at sticky spots called desmosomes. In pemphigus vulgaris immunoglobulin autoantibodies bind to a protein called desmoglein, which is found near the bottom of the epidermis. Resulting in keratinocytes separating from each other, and are replaced by fluid filled blister. Most individuals present with lesions on mouth and genitals, later blisters on the skin may develop. The most common mucosal area affected is the inside of the mouth but others include eyes, throat, labia, vagina, cervix, penis, urethra and anus. DHEA levels have been reported low in Pemphigus and Pemphigoid.

**Pemphigus Foliaceus:** In pemphigus foliaceus, blisters and sores do not occur in the mouth. Crusted sores or fragile blisters usually first appear on the face and scalp and later involve the chest and back.

**Diagnosis:** Nikolsky's sign is positive in Pemphigus. "This is present when pressure is put on the skin with the thumb, the epidermis appears to slide over the underlying dermis". This test is positive in pemphigus group of blistering dermatoses, a positive Nikolsky's sign can be seen in other bullous diseases such as toxic epidermal necrolysis and staphylococcus scalded skin syndrome. We consider all of these conditions to be autoimmune and responsive to IVIG treatment.

**Tests:** Biopsy Diagnosis generally requires a skin biopsy, which shows typical features of rounded-up separated keratinocytes within the blisters just above the bottom layer of the

epidermis. In most cases, circulating pemphigus antibodies (Anti-desmoglein-1 antibodies) can be detected by a blood test. E.S.R. is also elevated in pemphigus individuals. DHEA levels are low.

- **Treatment of Pemphigus:** Several studies have shown a high rate of response to minocycline treatment in Pemphigus especially oral pemphigus. A dose of 50 to 200 mg daily has been reported. Reversible hyperpigmentation of skin lesions can be seen which disappears after minocin is stopped. Minocin works in all types of Pemphigus (for pemphigus vulgaris, pemphigus foliaceus, or bullous Pemphigoid). Oral candidiasis may accompany minocin treatment yogurt supplements help. The best tolerated dose of minocycline is 100 mg daily. In the long run it can be changed to 100 mg on alternate days three times a week. 5-6 month of treatment is recommended.
- A low dose of prednisone needs to be given for a short time to control inflammation at 40 mg a day and can be tapered in two to three weeks to a lower dose and stopped.
- **Pyridostigmine** also known as mestinon is generally used for Myasthenia. However it has been found useful in all forms of Pemphigus. With the use of mestinon at a dose of 60mg three times a day, one can reduce the amount of steroid dose. **Dapsone** has also been found to be useful in the treatment of Pemphigus, especially in children it is used as a combination treatment with prednisone.
- It has been shown in multiple studies that IVIg is a treatment. The recommended dose is 400mg/kg on five consecutive days followed by one day monthly infusions for six months. Rather than go in detail the treatment is similar to CIDP and thus please read this in the neurology chapter.

**Bullous Pemphigoid (BP)** is a chronic blistering autoimmune disorder of the skin. Which can range from mildly itchy welts to blisters and infection, and may affect a small area or be widespread. Some individuals with BP have autoimmune diseases such as diabetes and rheumatoid arthritis. Exposure to drugs like furosemide, penicillin's, mechanical and physical trauma, burns from radiation, sun or heat, will increase the risk of getting Pemphigoid.

Bullous means a blister (a thin-walled sac filled with clear fluid). Usually the skin in BP is very itchy and large, red welts and hives may appear before or during the formation of blisters. The blisters are widespread and usually appear on the areas of the body that flex or move (flexural areas). About 15-20 percent of people with BP also develop blisters in the mouth or down the throat in the esophagus.

**Cicatricial Pemphigoid;** Cicatricial pemphigoid is a disease of the elderly. Lesions can arise on any mucous membrane surface including the nose, mouth, eyes, esophagus, larynx,

urethra and anal mucosal. Recurrent lesions will produce scarring gums are commonly involved and can cause gingivitis.

**Symptoms:** Small patches of itchy skin are typical. Blisters develop a week or more later. The blisters are quite firm, the fluid is usually clear, but may be blood-stained. Any area of skin can be affected but the arms, legs, armpits, and groin are the most common sites. The body may be covered in blisters but sometimes the blisters are in one area often on the lower leg. The inside of the mouth is rarely affected.

**Diagnosis:** Because of all the variations and differing degrees of symptoms, the diagnosis must be confirmed by skin biopsy. A special skin biopsy test (a direct immunofluorescence biopsy) may also be needed. Blood tests can show Pemphigoid antibodies.

**Treatment** is focused on relief of symptoms and prevention of infection.

- Tetracycline and Minocycline antibiotics are very useful for mild to moderate disease. They do not work on bacteria, but act directly on the immune system. They can be used in combination with potent topical steroid creams for more rapid relief. Several studies have shown a high rate of response to minocycline treatment in Pemphigoid. A dose of 50 to 200 mg daily has been reported. The side effect seen in some cases was a hyperpigmentation of skin lesions which disappeared after minocin was stopped. Minocin works in all types of Pemphigoid. Another side effect due to antibiotics can be oral candidiasis. The best tolerated dose of minocycline is 100 mg taken daily at bedtime with water only. After two weeks take, 100 mg on alternate days, total of three tablets a week. 2-3 month of treatment is recommended.
- Systemic corticosteroid therapy (prednisone 1 mg/kg/day) and azathioprine (2 mg/kg/day) the bullae rapidly disappear. The dose must be adjusted frequently, and side effects must be monitored. A fairly high dose is needed initially, and once the blisters have stopped appearing, it is slowly reduced over many months or years. As steroids have some undesirable side effects, try to reduce the dose as low as possible. If this is done too quickly, the blisters reappear.
- In resistant cases Dapsone can also be given in combination with steroids.
- IVIg is recommended for treatment at a dose of 400mg/kg on alternate days for 5 days and repeated at 400mg/kg every four weeks for five months. Please look under IVIg section for more details on IVIg dose guidelines.

**Lichen planus (LP):** Lichen planus is a relatively common autoimmune skin disease that comes in episodes. The onset may be gradual or quick. It is proposed that LP results from molecular mimicry to helicobacter pylori (Hp). It has been reported in several studies that Hp is associated with atrophic gastritis and LP. In a study done to test circulating basement membrane zone (BMZ) antibodies are present in erosive lichen planus (LP), it was shown that epidermal-binding BMZ antibodies were seen in 61% of the individuals.

The way this disease behaves by involving multiple sites in the body and coming in relapses and remissions. It has been associated with a number of other infections, Candida, hepatitis C. In a study of 303 individuals in Italy determined Anti-HCV circulating antibodies are more common in individuals with LP. Many autoimmune diseases occur with LP thus making the case stronger that LP is an autoimmune disease.

**Symptoms:** Lichen planus appears as shiny, flat-topped bumps that often have an angular shape. These bumps have a reddish-purplish color with a shiny cast due to a very fine scale. The disease can occur anywhere on the skin, but often favors the inside of the wrists and ankles, the lower legs, back, and neck. The mouth, genital region, hair and nails are affected in some individuals. Thick patches may occur, especially on the shins. Blisters may rarely occur. Bumps may appear in areas of trauma on some individuals. Lichen planus of the mouth most commonly affects the inside of the cheeks, gums and tongue. Oral lichen planus is more difficult to treat and typically lasts longer than skin lichen planus.

Oral lichen planus typically appears as patches of fine white lines and dots. This is associated with poor oral hygiene

**Tests:** Since the disease is associated with some infections a search for H. Pylori should be done and antibodies against H.Pylori need to be checked, oral Candida needs to be screened, history of exposure to Hepatitis C should be checked and antibodies against HCV need to be evaluated.

**Treatment:**

- H pylori if present needs to be treated and a course of metronidazole should be tried for a week. In a study a 95% response was seen in individuals treated with oral metronidazole, 500 mg twice daily, for 20 to 60 days and were followed up for a period of 5 to 36 months.
- Topical steroids such as betamethasone propionate ointments are generally applied for 4 week course. A thin smear rubbed in once a day and stopped when the lesions have flattened. Brown marks are often left at the sites, which take several months to fade. Steroid injections into affected areas may be useful for localized disease. In widespread disease prednisone 40 mg daily for two weeks and then tapered and stopped this will often clear up the lichen planus completely. Other treatments include long term antibiotics, oral antifungal agent, phototherapy, methotrexate and hydroxychloroquine. Tacrolimus ointment can be used.

**Rosacea:** Rosacea is a common autoimmune allergic condition characterized by symptoms of facial flushing and a spectrum of clinical signs, including erythema,

telangiectasia, coarseness of skin, edema, papules, pustules, ocular lesions and an inflammatory papulopustular eruption resembling acne. Rosacea affects mostly adults, usually people with fair skin, between the ages of 30 and 60. About 16 million Americans have this skin condition. Although it's more common in women, men may develop the disorder. Left untreated, rosacea tends to be progressive, which means it gets worse over time. Rosacea is remitting and relapsing which means it may flare up for a period of weeks to months and then signs and symptoms lessen for a while before rosacea flares up again.

**Rosacea fulminans** is a sub type of rosacea, which occurs exclusively in women well past adolescence. It's confined to the face, covering most of the surface with many fluctuant nodules and papules. Seborrhea prior to onset is typical. The individuals respond well to **isotretinoin** in combination with topical and systemic corticosteroids. The response is superior and much more rapid than in individuals treated with oral antibiotics. Rosacea fulminans is an indication for topical or systemic corticosteroids.

**Rhinophyma** develops when severe rosacea is left untreated over a long period of time. The papules gradually increase in size. When these nodules converge on the nose, they give the nose a swollen, red appearance.

We consider all the subtypes of Rosacea as autoimmune so we present the treatment together. Increased prevalence of *Helicobacter pylori* (Hp) infection in individuals with rosacea, with some evidence of dermatological improvement in individuals treated with antibiotics for this infection. Immune-responses against *H. pylori* antigens have been demonstrated and reported in Rosacea individuals. In a study on Rosacea individuals after eradication of Hp, 51 out of 53 treated rosacea individuals became Hp negative. The symptoms of rosacea disappeared in 51 individuals, markedly declined in one and remained unchanged in one individual. Conclusion from this study is that Hp eradication helps a majority of individuals with Rosacea.

The eradication of Hp leads to a dramatic improvement of symptoms of rosacea and reduction in related gastrointestinal symptoms, gastritis, and gastric acid secretion; Rosacea could be considered as one of the major extra gastric symptoms of Hp infection probably mediated by Hp related cytotoxins and cytokines.

Young women who are taking a multivitamin a day may develop Rosacea. If they stop the vitamin in time the rosacea will go away. Rosacea is associated with daily high dose intake of vitamin B-12 and B-6.

**Symptoms:** Rosacea starts with facial flushing which like any other autoimmune condition comes in attacks. If the condition is not treated it takes other forms and telangiectasia, coarseness of skin, edema, papules, pustules, all may form.

**Test:** Antigliadin antibody, antithyroid antibodies

**Treatment:**

- Typical 1 wk anti-Hp therapy including omeprazole (20 mg bd.), clarithromycin (500 mg bd.) and metronidazole (500 mg bd.)

- Systemic and topical remedies may be used to treat the papulopustular of rosacea. Systemic treatment includes metronidazole, doxycycline, **minocycline**, and clarithromycin. If the individual does not respond to the topical antibiotic then oral antibiotics are recommended.
- Topical metronidazole cream and gel are used for papulopustular rosacea.
- Ocular involvement is common in individuals with cutaneous rosacea and can be treated with orally administered or topical antibacterials.
- Once rhinophyma starts the only treatment is by surgical or laser.
- Individuals need to follow a strict diet, wearing hats in the sun and scarves in the cold to control the disease triggers. Regularly applying topical medication should help most individuals. Avoid too much exercise, avoid alcohol, and avoid too much makeup, hot baths, steroids, spicy foods, stress anger and embarrassment.

**Livedoid vasculopathy:** Livedoid vasculopathy (LV) is a chronic autoimmune vascular disorder characterised by persistent painful chronic ulceration of the feet. Peripheral spider veins (telangiectasia) and increased pigmentation (hyperpigmentation) white atrophic scars on the dorsum of the feet. The condition occurs with first in leg or feet and can spread to the abdomen and hands accompanied by a neuropathy. These ulcerations are often recurrent and chronic with spontaneous remissions and exacerbations which may be seasonal, increased incidence during the winter and summer months. LV occurs most commonly in middle-aged women. The disease has been observed in individuals with factor V Leiden mutation, antiphospholipid antibody syndrome, hyperhomocysteinemia, protein C deficiency, and increased platelet activation, all of these conditions are increase risk of blood clotting.

**Symptoms:** Pain with hyperpigmented lesions producing a livedoid pattern, ulcerations on both ankles and white atrophic scars on the dorsum of the feet.

**Case report:** A 49-year-old woman with livedoid vasculopathy. The individual presented with an elevated homocysteine level caused by renal insufficiency, vitamin-B6 deficiency and reduced vitamin-B12 concentration. Vitamin treatment reversed her condition.

**Tests:** Biopsy demonstrates a increased blood vessels formation and vessel occlusion with erythrocytes. The small number of leukocytes and the lack of nuclear fragments around the small vessels are the most important signs. Low vitamin B-6 level, low folic acid level, low vitamin B-12 level and high homocysteine levels. CRP is elevated.

#### **Treatment:**

- Therapies that benefit include aspirin, coumadin, dipyridamole (5), low molecular weight heparin (6), pentoxifylline (7), enoxaparin (3), nifedipine (8), and tissue plasminogen activator (9). In addition, tobacco cessation should be advised.
- Along with sublingual replacement of B-12, folic acid and vitamin B-6.

## **Chapter 10 Rheumatic Autoimmune**

**Rheumatoid arthritis (RA):** Rheumatoid arthritis is an autoimmune disease triggered by mycoplasma, bacteria or virus. It is two to three times more common in women than in men and generally strikes between the ages of 20 and 50. Rheumatoid arthritis can also affect children. The diagnosis is based upon clinical examination and elevated sedimentation rate or CRP along with x-rays showing early damage in the joints.

Investigators have shown that mycoplasma which is a small bug without a cell wall causes arthritis in humans. In 1949 at the International Congress on Rheumatic Diseases reported the possible relationship between mycoplasma and joint disease. National Institutes of Health (NIH) issued a research grants in 1950, to Thomas Brown, M.D., he reported an immunologic reaction of antigen and antibody (with mycoplasma as the suspected antigen) as the cause of rheumatoid disease. Further support of mycoplasma as a causative agent and antigen was proven; in 1964 a high incidence of mycoplasma antibodies in the blood of rheumatoid arthritis individuals and lupus individuals was found. Also recognized was a 4:1 higher incidence of mycoplasma antibodies in females suggesting a correlation with the higher incidences of rheumatoid arthritis in females. In 1989, NIH requested grant applications for the controlled clinical trials of tetracycline therapy for rheumatoid arthritis. The preliminary results of the clinical trials, known now as MIRA or Minocycline in Rheumatoid Arthritis, were promising and the NIH requested grant applications for studies of mycoplasma as causes for rheumatoid diseases in 1993 and for a study for intravenous antibiotics for rheumatoid arthritis in 1994. The result of the MIRA clinical trial stated, "Individuals who suffer from mild to moderate RA have the choice of another therapeutic agent. The antibiotic significantly reduces symptoms, the side effects were minimal. A review on Tetracycline's treatment of ten randomized controlled trials including 535 individuals were reviewed, reviewers reported minocycline was associated with a clinically improvement in disease activity in RA with no absolute increased risk of side effects.

#### **Symptoms:**

- § Pain and swelling in your joints, especially in the smaller joints of your hands and feet
- § Generalized aching or stiffness in joints after sleep or after periods of rest
- § Reduced motion of the affected joints
- § Weakness in muscles attached to the affected joints
- § Fatigue, which can be severe during a flare-up
- § Low-grade fever
- § Deformity of your joints over time
- § General sense of not feeling well (malaise)

Early in rheumatoid arthritis, the joints in the wrists, hands, feet and knees are most often affected. Later in the disease, shoulders, elbows, hips, jaw and neck can be involved. It generally affects both sides of your body at the same time. Small lumps, called rheumatoid nodules, may form under the skin at pressure points and can occur at your elbows, hands, feet and Achilles tendons.



**Test:** Check CRP and ESR both are elevated. Check for Mycoplasma antibodies, IgG levels and IgG sub-class levels.

**Treatment: What precaution to use:** Limiting sugar and grains is a critical element of the treatment program. Individuals who are unable to decrease their sugar intake are less likely to improve with the antibiotic protocol. All individuals need to go on a pure vegetable, fruit, rice, milk, beef, chicken and fish diet. No alcohol, no beer, and no sugar, only honey is allowed in this diet.

**Antibiotic Therapy: What antibiotic to give for reactive arthritis:**

- **Minocin** 100 mg. is taken on alternate days should be given three tablets a week. Doxycycline can be substituted for individuals who cannot obtain Minocin. It is important to take medication on alternate days, as long term use of the drug can cause toxicity. Tetracycline type drugs can cause a permanent yellow brown discoloration of the teeth. This can occur in last half of pregnancy and in children up to eight years old. One should not routinely use tetracycline in children. If individuals have severe disease, one can consider increasing the dose to as high as 200 mg three times a week. Minocin can cause nausea and vertigo, taking the dose at night does help to decrease this problem. If one encounters a resistant form of rheumatic illness, intravenous administration should be considered. Most people take the doses at night every Monday, Wednesday and Friday.
- **Clindamycin:** It is important to use the intravenous (IV) form of treatment if the disease is severe. Scleroderma is a particularly severe form of rheumatic illness that should receive IV treatment. Individuals with long standing disease are started with daily intravenous clindamycin for five days. The first two days, 300 mg. of clindamycin are given in 250 cc 0.9% saline infused over an hour. (D5W solution is avoided due to yeast overgrowth seen in individuals). The third and fourth day if the individual tolerates 600 mg. is given, if the individual can tolerate the fifth and subsequent days 900 mg is used. After the initial daily intravenous series, IVs may be administered once weekly or once every other week or as the physician determines for the individual. The IVs are continued until all lab figures return to normal, which may take longer than a year, sometimes several years for individuals with severe or long standing disease. Lab results should then be monitored for several months longer, to be sure that the individual remains stable, before discontinuing the IV. Clostridium-difficile-pseudomembranous-enterocolitis can result by administration of clindamycin. Uncontrollable diarrhea results with the use of antibiotics, to avoid this use acidophilus or yogurt which promotes the growth of the healthy gut flora. Clindamycin can also be taken orally, or in intramuscular injections. Orally, the single dose is 1200 mg. once a week. For intramuscular injections, 300 -600 mg. taken once a week can be used. For sensitive individuals, a local anesthetic may be applied to the injection site. Changing the needle tip, after drawing the medication into the syringe and before injecting, will avoid the problem of tissue irritation at

the injection site, because it is the trace amount of medication on the tip of the needle that causes the tissue irritation.

- **Prednisone:** Individuals with severe disease can use prednisone 5 mg daily. They can take one tablet a day if they develop a severe flare-up as a result of going on the antibiotics. They can use an additional tablet at night if they are in really severe flare. This is the first medicine they should try to stop as soon as their symptoms permit. Usually one lowers the dose of prednisone by about 1 mg per week. If a relapse of the symptoms occurs, than further reduction of the prednisone is not indicated. Blood levels of cortisol peak between 3 and 9am. It would, therefore, be safest to administer the prednisone in the morning. The most significant side effect of steroids is osteoporosis. Other side effects that usually occur at higher doses include adrenal insufficiency, cataract formation, Cushing's syndrome, diabetes, ulcers, herpes simplex and tuberculosis reactivation, insomnia, hypertension, myopathy, mood disorders and renal stones.
- One also needs to be concerned about the increased risk of peptic ulcer disease when using this medicine with conventional non-steroidal anti-inflammatories. Persons receiving both of these medicines may have a 15 times greater risk of developing an ulcer. Use Magnesium supplements and drink milk or take yogurt between meals to help reduce the chances of stomach ulcers.
- Those individuals not responding to above treatments need to look under treatment guidelines under CIDP section especially medications mentioned under **list-A**.

**Remission:** The disease seems to be controlled if the morning stiffness, joint pain, joint swelling becomes less. It can also be checked by the lowering of the WBC and sedimentation rate.

**Dr. Brown successfully treated over 10,000 individuals with this protocol. He found that significant benefits from the treatment.** In some individuals the above protocol may not work they should follow the treatment guidelines for CIDP. Generally steroids, Remicade, non steroidal will help control symptoms. Stiffness can be reduced by using colostrum 400-500 mg twice a day. This dose can be taken three or four times a day.

**Ankylosing Spondylitis (AS):** This type of autoimmune arthritis primarily affects the spine, but may also cause arthritis in the hips, shoulders, and knees. The hallmark feature of AS is the involvement of the joints at the base of the spine where the spine joins the pelvis the sacroiliac (SI) joints. The tendons and ligaments around the bones and joints in the spine become inflamed, resulting in pain and stiffness, especially in the lower back. Ankylosing spondylitis tends to affect people in late adolescence or early adulthood. Eighty percent of the individuals are positive for HLA B-27. The disease course is highly variable, and while some individuals have episodes of transient back pain only, others have more chronic severe back pain that leads to differing degrees of spinal stiffness over time. In almost all cases the disease is characterized by acute painful episodes and remissions (periods where the problem settles). Infections were relatively common in three months leading to the first symptoms. Infections are usually respiratory, gastrointestinal or urinary. Heavy physical activity, work stress, pregnancy, injury and surgery have also been reported as probable triggers of this disease.

**Symptoms:**

- Chronic back pain for many months.
- Back pain during the night. (less distractions raise the pain level at night)
- Back stiffness lasting for extended periods in the morning or after periods of rest.
- Pain and tenderness in the ribs, shoulder blades, hips, thighs, shins, heels and spine.
- Recurring eye inflammation, redness, blurred vision, and sensitivity to bright light
- Improvement with exercise and motion
- Spinal stiffness in the mornings

**Test: X-Ray** of the spine shows a bamboo spine due to deformed vertebral bodies into an abnormal square shape. CRP & E.S.R. are elevated.

**Please see the treatment guidelines under the rheumatoid Arthritis section.**

**Osteoarthritis (OA):** Osteoarthritis appears to behave like an autoimmune disease, used to be called a degenerative joint disease; it is the most common form of arthritis. About \$50 billion a year is spent on medical costs. Many studies have shown inflammation involved in OA, and it has been renamed as a reactive arthritis. Osteoarthritis is characterized by the breakdown of joint cartilage and may affect any joint in the body, including the little finger joints, large hips, knees, lower back and feet. Initially osteoarthritis may strike only one joint, later multiple joints may become arthritic. For twenty years we have seen individuals with inflamed joints and placed them on anti-inflammatory treatments including steroids. These OA individuals respond to anti inflammatory treatments including steroids, if CRP is measured it is elevated in all individuals with active arthritis. The time has come to call OA an autoimmune disease. Antibodies against joint cartilage proteins were first reported in 2000 in OA, an IgG-type anti-TPI autoantibodies (triosephosphate isomerase antibody) are detected in the synovial fluid samples from the individuals with OA, produced by the antigen-driven mechanism, this has a potential to be used as a diagnostic marker for OA. The presence of an antibody is enough proof to consider OA as an autoimmune arthritis. Salmonella, Yersenia infections are frequently associated with osteoarthritis; we consider OA as autoimmune arthritis which is caused by molecular mimicry thus treatment should be similar to other autoimmune arthritis.

**Symptoms:**

- Pain in a joint during or after use, or after a period of inactivity
- Discomfort in a joint before or during a change in the weather
- Swelling and stiffness in a joint, particularly after using it
- Bony lumps on the middle or end joints of your fingers or the base of your thumb
- Loss of joint flexibility

**Tests:** CRP level, X-ray joints which shows loss of joint space. The diagnosis is made on clinical examination of swollen joints.

**Treatment:** Tetracycline's have recently been shown to have "chondroprotective" effects in inflammatory arthritis. Following 16 months of treatment in a recent study, results indicated that the average loss of joint space in the affected knee was 40% less among participants taking doxycycline than those who took placebo. Giving a small injection of steroids with 1% lidocaine in the joint space, is helpful in reducing pain and inflammation. **Please see treatment guidelines under rheumatoid arthritis section.**

**Psoriasis** is a chronic, inflammatory autoimmune skin disease. Involving knees, elbows, scalp, trunk, and nails are the most commonly affected areas. The inflamed skin cells are thought to cause the silvery white scales that are characteristic of plaque-type psoriasis. There are several types of psoriasis.

**Symptoms:** The red, thickened and rough patches of psoriasis may occur anywhere, but are commonly found on the scalp, elbows, knees, palms and soles. Other symptoms include:

- Silvery white scales
- Pitted or dented fingernails and/or toenails
- Red lesion in the folds of the buttock abdomen, face and arms
- Joint pain suggesting arthritis
- Numbness in feet (neuropathy)

### **Types of psoriasis**

- **Guttate psoriasis:** Is usually triggered by a bacterial infection such as strep throat. Usually repeated episodes of skin lesions like sores are seen on trunk, arms, legs and scalp, especially with ongoing sub-clinical streptococcal throat infections.
- **Plaque psoriasis:** Plaque psoriasis is the most common presentation of psoriasis and affects the typical areas of the elbows, knees, umbilicus and lower back.
- **Pustular psoriasis.** A rare form of psoriasis occurs in patches over hands, fingertips or feet. Pus filled blisters appear after the skin becomes red and tender. Blisters may reappear several times accompanied by, chills, itching, weight loss, fever and fatigue, accompanied by sub-clinical streptococcal infections.
- **Inverse psoriasis.** The areas in the armpits, groin, under the breasts and buttocks, patches of red, inflamed skin are seen. Common in overweight people and is exacerbated by friction and sweating.
- **Erythrodermic psoriasis.** May be triggered by sunburns, by steroids and medications, peeling red rash develops over the whole body that may itch or burn.
- **Psoriatic arthritis.** Psoriatic arthritis causes pitted, discolored nails and the swollen, painful joints and conjunctivitis. Symptoms range from mild to severe. Stiffness and joint damage is seen.

**Diagnosis:** There are no specific blood tests or diagnostic procedures for psoriasis. Sometimes a skin biopsy will be done to confirm the diagnosis. ESR and CRP are elevated or normal. Rarely a skin biopsy may be done.

**Treatment:**

- **In Guttate** the psoriasis is associated with tonsils infection. If repeated attacks of tonsillitis occur consider removing the tonsils. Streptococcal throat infections can cause exacerbation of chronic plaque or guttate psoriasis. Psoriasis individuals should report sore throat to their physician and that early treatment of streptococcal throat infections will benefit from penicillin. Benzathine penicillin 1.2 million units, was given I.M. every two weeks. After 24 weeks Benzathine penicillin is reduced to 1.2 million units once a month used up to two years.
- **Vitamin D:** It is used in the treatment of moderate psoriasis. This cream, ointment, or solution is applied to the skin 2 times a day.
- **Coal Tar:** Coal tar is applied topically and is available as shampoo, bath oil, ointment, cream, gel, lotion, ointment, paste, and other types of preparations. The tar decreases itching and slows the production of excess skin cells.
- **Corticosteroids:** These creams or ointments are usually applied twice a day, but the dose depends on the severity of the psoriasis.
- **Tree Bark Extract.** Apply the cream, ointment, or paste sparingly to the patches on the skin. On the scalp, rub into affected areas. Avoid the forehead, eyes, and any skin that does not have patches. Do not apply excessive quantities.
- For arthritis treatment please see the rheumatoid section, for a list of other drugs please see the CIDP treatment section.

**Reactive Arthritis and Reiter's Syndrome:** Reiter's syndrome, is a autoimmune arthritis, is a clinical triad of urethritis, conjunctivitis, and arthritis. Reactive arthritis usually begins one to four weeks after a urinary or gastrointestinal tract infection. Causative organisms include Chlamydia, Ureaplasma, Shigella, Salmonella, Yersinia, and Campylobacter species. The arthritis tends to involve a single joint, preferentially affecting the joints of the lower extremities. It is of sudden onset, within a few days, many painful and swollen joints develop in an asymmetric distribution. Weight loss and fever has been seen in people with reactive arthritis. Persons with HLA-B27 are at increased risk for developing Reiter's syndrome after sexual contact or exposure to certain enteric bacterial infections.

**Symptoms:**

- Acute diarrhea frequently is a presenting manifestation with Shigella, Yersinia, or Salmonella infection. The diarrhea precedes the appearance of musculoskeletal symptoms by up to one month.
- Conjunctivitis (red-eye) is present in up to 50 percent of individuals
- Urethritis is non-infectious type, the urethritis may be mild or severe.
- Oral ulcers are common and may be painless, and a painless lesion of the glans penis, is present in males individuals with reactive arthritis.
- Skin lesions on palms of the hands or the soles of the feet.

**Test:** HLA-B27 gene is present in most individuals, ESR is elevated, and Chlamydia antibodies may be present.

### **Treatment**

- Begins with NSAIDs. Sulfasalazine has been shown to be effective in individuals with chronic reactive arthritis. Intra-articular corticosteroid injections can be effective in controlling disease in individual joints.
- Because of the bacterial etiology in reactive arthritis, there has been a possible role of antibiotic therapy in individuals with the disease. Treatment options for uncomplicated urogenital infections include a single 1-g dose of azithromycin orally, or doxycycline at a dosage of 100 mg orally twice per day for seven days.
- For conjunctivitis use an either oral doxycycline or Erythromycin ophthalmic ointment can be used.
- Antibiotic therapy has not been effective in several trials, but please read treatment in rheumatoid-arthritis section as may benefit some cases.

**Scleroderma & C.R.E.S.T:** Scleroderma is an autoimmune disease that can cause thickening, hardening, or tightening of the skin, blood vessels and internal organs. Scleroderma is chronic, which means it can last a long time. This is one disease in which the individuals never gain weight, due to the effect it has on tightening their skin they all look skinny. They also have very hard hands, with skin around the fingers tight. They have difficulty swallowing as the esophagus is tight, so is the stomach wall tight and they cannot tolerate large meals. There are two types of scleroderma localized and systemic.

**a-Systemic Scleroderma (SS)** also called systemic sclerosis, the immune system causes inflammation in the small blood vessels and the collagen-producing cells located in the skin and throughout the body. SS causes the small blood vessels in the fingers to be inflamed, this causes injuries on the hands and fingers to heal slowly. In severe cases, ulcers form on the hands and fingers. People with Systemic Scleroderma are usually cold-sensitive. The inflamed small blood vessels and the reduced blood supply cause cold temperature sensitivity. Systemic Scleroderma individuals also have problems with their heart, lungs and gastrointestinal tract. These problems occur as tissue builds up in the skin and organs for after inflammatory.

**b-Localized Scleroderma** Localized Scleroderma is called Morphea affects the collagen-producing cells in just some areas of the body, and usually does not affect the internal

organs and blood vessels. Localized Scleroderma can be seen as patches of thick skin or as a line of thick skin. The line may extend down a leg or arm.

A sub type of scleroderma is called **CREST** has a distinct set of characteristics that give the syndrome its acronymic name. These characteristics include:

- **Calcinosis.** Tiny calcium deposits form under your skin, on elbows, knees and fingers, can occur almost anywhere, in the body.
- **Raynaud's phenomenon.** Due to inflammation in the blood vessels the hands become cold.
- **Esophageal dysfunction.** Due to tightness of the stomach and swallowing tube (esophagus) the swallowing and retention of fluids in the stomach is difficult.
- **Sclerodactyly.** Thick hard skin starts to calcify. This bone like hard areas can be seen on X-ray and visually.
- **Telangiectasia.** Small blood vessels start to form on lips and fingers look like small spiders.

#### **Treatment:**

- **Minocin** has been reported to reverse the clinical findings in this disease and stop all further progression. A dose of 100 mg at night should be taken without food and lots of water. Treatment should continue over several months, three month minimum. **For the complete protocol see the rheumatoid arthritis section.**
- Nifedipine, in dosages ranging from 30 to 60 mg daily, reduces the severity of Raynaud phenomenon and cold intolerance. Nifedipine is well tolerated, and the most common adverse effects are headaches, flushing, and edema of the feet and ankles. Pentoxifylline (400 mg, 3 times daily), alone or in combination with nifedipine, reduces blood viscosity by increasing red blood cell deformability and can be used to improve capillary function.

**Autoimmune Vasculitis:** Vasculitis is described as an inflammation within the blood vessels. In all case this inflammation is autoimmune. Inflammation within the wall of the blood vessels will cause thickness of the vessel; inflammation in the lumen will cause thrombosis or occlusion of the vessel. These individuals have symptoms which remit and relapse in cycles. Inflammation of blood vessels in the heart may cause heart attacks and in the brain result in strokes.

**Giant Cell Arteritis, GCA** (temporal arteritis) or **AION:** The optic nerve is an extension of the brain that connects the retina of the eye to the brain. The retina contains photoreceptors, cells that are activated by light and that connect to other retinal cells called ganglion cells. These, in turn, send information through projections called axons into the brain. By this route, the optic nerve gets visual impulses to the brain. Ischemic optic neuropathy, or "stroke of the optic nerve" also causes loss of vision in one eye can be

autoimmune in most cases. **Anterior ischemic optic neuropathy ( AION)**, may be caused due to acute loss of blood flow and ischemia to the front (anterior) part of the optic nerve (also called optic nerve head), which is supplied mainly by blood vessels called posterior ciliary arteries. The stroke is usually caused by inflammation in the blood vessels due to vasculitis triggered by the immune system. GCA is the most common form of vasculitis in the elderly usually seen in older women who present with a history of difficulty in chewing, headaches, scalp lesions and have large dilated temporal arteries. The individuals will not touch the scalp as it hurts and they stop combing their hair. They will point to the area of the pain without touching it. The diagnosis is secured by a elevated **E.S.R.** This condition is a medical emergency if not treated the individual can go blind. Remember these are long term conditions and individuals have to be treated for years. The most important complication of giant cell arteritis is visual loss in one or both eyes due to AION or retinal artery occlusion. Usually, visual loss is irreversible even with therapy.

**Symptoms:** Several instances of amaurosis fugax (transient blindness) may precede the blindness by up to six months Individuals may have a new-onset headache, Pain on chewing may be unilateral, but it is more often bilateral (jaw claudicating), shoulder or hip pain (proximal myalgia), weight loss, and fever may lead to the diagnosis. Loss of vision in the affected eye with pupil reacting poorly to light reflex is diagnostic of an optic nerve lesion, in retinal or optic nerve disorders, if we shine light on the normal eye that pupil constricts, and then shine the light on the bad eye, instead of constricting the pupil dilates immediately in the bad eye. That is what is called a relative afferent pupillary defect. Some individuals notice mini episodes of visual loss called amaurosis fugax while they are chewing food.

**Laboratory Tests:** Erythrocyte sedimentation rate is elevated, CRP is high, and anti-cardiolipin antibodies may be positive in arteritis, but none of this proves the diagnosis. Temporal artery biopsy is the gold standard for diagnosis of giant cell arteritis. Due to skip lesions, a negative result does not exclude the diagnosis. Homocysteine levels can be checked to look for elevation.

**Treatment:** Corticosteroid (prednisone) is the drug of choice to treat giant cell arteritis. Therapy is required for a long time, monitored by parameters of inflammation (ESR, CRP). A viral cause has been suspected but not confirmed in giant cell arteritis. An increased prevalence of antibodies against parainfluenza virus type 1 was reported in individual's giant-cell arteritis. Long term treatment is recommended with monthly monitoring of E.S.R. Using aspirin one a day is recommended.

**Takayasu arteritis** was first described by a Japanese Dermatologist is a chronic inflammatory condition that affects the largest blood vessel in the body (the aorta) and its branches. The “typical” individual with Takayasu’s arteritis is a woman under the age of 40. Takayasu’s arteritis is occasionally called “pulseless disease”, because of the difficulty



in detecting peripheral pulses that sometimes occurs as a result of the narrowing of the blood vessel. Then the young woman may present with headaches. On examination individuals will usually have loss of pulses in arms and bruits in the neck. Large blood vessels are inflamed and sedimentation rate or CRP is elevated. These individuals usually go to the neurologist seeking attention for headaches. The disease has been known to get worse after pregnancy and undiagnosed individuals will develop stiffness and difficulty walking. Rarely severe stenosis in the subclavian artery will result in blood pressure difference between two arms, more than 15mm/Hg difference. Stenosis of subclavian will also cause mini strokes causing spinning type feelings. Mini strokes called TIA may cause shining spots in the vision which may last upto hours.

**Symptoms:** Most young women present with complaints of headaches and sometimes they start to see shining objects in their eyes without a headache. Some will have complaints of arm pain, weakness and tiredness. Individuals complain of generalized fatigue. Some may hear a noise in their ear. Usually no pulses can be felt in the arms and on listening for bruits many are present in the neck and thighs. Blood pressure cannot be obtained in the arms.

**Test: CRP and Sed arte are elevated.** Carotid ultrasound will show a swelling in the wall of the carotid artery. MRI angiogram can show inflammation in the subclavian arteries.

### **Treatment of Takayasu:**

- A study done in Japan on twelve individuals used **Minocycline 100mg twice a day for three months**. All the individuals responded to treatment and nine went into complete remission of the disease. Another author reported improvement with **Clarithromycin** in his individual and reported improvement. Important medication to give is a Asprin to prevent mini strokes daily, and Fish oil twice a day to reduce inflammation. We do not recommend surgery if there is severe stenosis I/V steroids or IVIg can be used to reduce inflammation.
- **Disease responds well to prednisone and methotrexate.** Prednisone is started at 30 mg a day and the E.S.R. is monitored, dose is adjusted based upon the E.S.R. It is best to maintain the sedrate below 15mm/hr. (Please see the CIDP treatment section for a list of all the drugs which can be sued in autoimmune conditions).
- In all the Vasculitis inflammation can be reduced by giving IVIg. Intravenous immunoglobulin (IVIg) is a potential alternative treatment for treatment anti-neutrophil cytoplasm antibody (ANCA)-associated systemic vasculitis (AASV) with less toxicity than conventional immunosuppressive agents. This randomized, placebo-controlled trial aimed to investigate the efficacy of a single course of IVIg (total dose 2 g/kg) in previously-treated AASV with persistent disease activity in whom there was an intention to escalate therapy. Following the trail CRP levels were reduced after IVIg treatment and the effect lasted about three months.

- Another trial done at St George Hospital with IVIg this time in Wegener's granulomatosis resulted in all six individuals improving. IVIg was well tolerated and all six individuals had early reductions in disease activity. Four entered full, clinical remission which lasted for at least 1 yr, while in two the responses were partial and transient, and they subsequently required conventional treatment. After 16-48 months of follow-up, two of the four individuals in full remission relapsed, but the other two have remained well.
- Fish oil up to 1 gram daily with an Asprin should be used by all individuals unless there are contraindications like stomach ulcers or bleeding disorders which can get worse by using Asprin.

**Behcet's Disease (BD):** This autoimmune disease was first described by a Turkish dermatologist in 1930. Behcet's disease is most common along the "Old Silk Route", which spans the region from Japan and China in the Far East to the Mediterranean Sea, including countries such as Turkey Afghanistan, Pakistan and Iran. In Japan this is the commonest cause of Blindness.

Behcet's disease involves blood vessels of all sizes and types, and involving veins as well as arteries. Because of the diversity of blood vessels it affects, manifestations of Behcet's may occur at many sites throughout the body. Recently (BD) has been associated with and *Helicobacter pylori* (HP), in a study of 13 individuals with BD, the number and size of oral and genital ulcers diminished significantly and various clinical manifestations regressed after the eradication of HP.

**Symptoms** of Behcet's disease include recurrent ulcers in the mouth (resembling canker sores) and on the genitals, with eye inflammation. The disorder may also cause various types of skin lesions, arthritis, bowel inflammation and encephalitis (inflammation of the Brain, which can cause confusion and loss of consciousness or seizures).

**Test: E.S.R. is elevated,** check for H.Pylori antibodies.

**Diagnosis:** A criteria put forth by a international group to help diagnose includes,

- Recurrent oral ulceration (at least three occasions in a year). In addition, a individual must also meet two of the following four criteria for Behcet's disease:
- recurrent genital ulcerations,
- eye inflammation (uveitis or retinal vasculitis),
- skin lesions (erythema nodosum, lesions, acne),
- Positive "pathergy test". The pathergy test is a simple test in which the forearm is pricked with a small, sterile needle. Occurrence of a small red bump or pustule at the site of needle insertion constitutes a positive test. Although a positive pathergy test is helpful in the diagnosis of Behcet's, only a minority of Behcet's individuals demonstrate the pathergy phenomenon

**Treatment: We recommend using omeprazole (20 mg bd.), clarithromycin (500 mg bd.) and metronidazole (500 mg bd.) For two weeks.**

- For disease that is confined to (mouth, genitals, and skin), Azithromycin was observed to be effective in decreasing folliculitic lesions and fastening the healing

time of oral ulcers in BD topical steroids and non-immunosuppressive medications such as colchicine may be effective. Some individuals require chronic, low doses of prednisone to keep the disease under control.

- In the event of serious end-organ involvement such as eye or central nervous system disease, both high doses of prednisone and some other form of immunosuppressive treatment with azathioprine, cyclosporine, cyclophosphamide or chlorambucil.
- Neurological events such as Transverse Myelitis (Inflammation of spinal cord): use steroids, cyclophosphamide, or interferon-alpha. For more detailed treatment look under CIDP.

**Churg-Strauss Syndrome (CSS):** is an inflammation of blood vessels (vasculitis). This disease was first described in 1951 by Dr. Churg and Dr. Strauss A rare type of vasculitis which is often preceded by a history of **asthma**, and the disease begins with sneezing and nasal congestion (allergic rhinitis), often with nasal polyps and sinusitis. If steroids doses are reduced quickly in asthmatics it can result in the development of CSS.

**Symptoms** are asthma-like respiration. There is fever, involvement of skin, kidney and lung with eosinophilia. Later it may cause a neuropathy with numbness and pain.

**The Criteria for diagnosis must have any four of the following findings.**

- Asthma;
- Eosinophilia; (Blood cells which cause allergy)
- Mononeuropathy; (dysfunction of a single nerve, facial palsy, hand weakness or drop foot)
- Temporary infiltrates on chest X-rays;
- Paranasal sinus abnormalities. (Infection or inflammation in sinuses)

**Test: ESR** also called (erythrocyte sedimentation rate) is usually elevated. **IgE** is elevated. Skin and Food allergies need to be tested. Rarely Celiac disease has been associated with CSS test for antigliadin antibody and H.pylori antibodies.

**Treatment:** CSS responds to prednisone. Initially, 40 mg/day prednisone is used. After 1-2 weeks this high dose of prednisone is gradually tapered down. Other immunosuppressive drugs, such as azathioprine, cellcept, methotrexate, or cyclophosphamide may be used. In cases which are resistant to treatment will greatly benefit from IVIg. It works well if there is multi organ involvement. Please see the IVIg section for dosing information. Omalizumab is a recombinant humanized monoclonal antibody directed against immunoglobulin E (anti-IgE) to inhibit the immune system's response to allergen exposure, Omalizumab may become a useful tool for the treatment of CSS.

**WEGENER'S** is uncommon necrotizing vasculitis, with tumor like inflamed lesions called granuloma; these lesions are seen in the entire respiratory tract, with kidney dysfunction called (glomerulonephritis). The lesions closely resemble those in polyarteritis nodosa. Gum tissue grows thick with distinctive red and granular appearance of the gums

(strawberry gingival) due to inflammation is visible. Rarely inflammation of the lacrimal gland is the first presenting symptom.

**Symptoms** are weakness, tiredness, weight loss, sinusitis, joint pains (polyarthralgia), ulcerations of the nasal septum, signs of renal disease, and fever. The disease occurs in young adults. Either sex may be affected. Death occurs in a matter of months, most often from kidney damage. Individuals can present at age 80 with sinusitis unresponsive to antibiotic treatment.

**Test:** E.S.R. is elevated CRP and is elevated and slightly elevated c-ANCA (cytoplasmic-antineutrophil cytoplasmic antibody). Individuals with the limited form of Wegener's granulomatosis are occasionally seronegative and respond well to therapy.

**Treatment** The first drug to try is Cotrimoxazole (Septra or Bactrim) Sulfamethoxazole and trimethoprim combination is used to treat infections, such as bronchitis, middle ear infection, urinary tract infection, and traveler's diarrhea. It is also used for the prevention and treatment of *Pneumocystis carinii* pneumonia (PCP) which contain. Cotrimoxazole seems to reduce the number of relapses in individuals with this chronic disease at a dose of one tablet twice a day. **This can lead to complete clinical remission.** Dramatic improvement is seen with oral cyclophosphamide and prednisolone. Those who are unresponsive to above treatment may respond to cyclosporine. (More in the renal section)

**Sjogren's** syndrome is an autoimmune disorder in which immune cells attack and destroy the glands that produce tears and saliva. Sjogren's syndrome is associated with rheumatic disorders such as rheumatoid arthritis, may affect other organs of the body including the kidneys, blood vessels, lungs, liver, pancreas, and brain. In some cases this also causes a autoimmune neuropathy which should be considered as C.I.D.P. (treatment described in the neurology chapter). Sjogren's syndrome affects 1-4 million people in the United States. Most people are more than 40 years old at the time of diagnosis. Women are 9 times more likely to have Sjogren's syndrome than men.

**Symptoms:** The hallmark symptoms of the disorder are dry mouth and dry eyes. In addition, Sjogren's syndrome may cause skin, nose, and vaginal dryness. There may be numbness in the feet or hands and arthritis with fatigue.

- Dry mouth, dry eyes, Dental cavities
- Fatigue and Fever
- Enlarged parotids which is a salivary gland, located behind the jaw and in front of your ears , Difficulty swallowing or chewing
- Change in sense of taste , Hoarseness
- Oral yeast infections, such as candidiasis
- Irritation and mild bleeding in your nose
- Skin rashes or dry skin , Vaginal dryness
- Dry cough that doesn't produce sputum
- Joint pain, swelling and stiffness

**Test:** H.Pylori antibodies usually present, ESR is elevated and so is the CRP. ANA antibodies are usually positive. Antibodies specific to Sjögren's syndrome (SS): anti-SS-A and SS-B; is (usually positive)

**Treatment:** We recommend using omeprazole (20 mg bd.), clarithromycin (500 mg bd.) and metronidazole (500 mg bd.) For two weeks. For the treatment of arthritis in Sjogren's please see the guidelines described under rheumatoid arthritis section. Artificial tears are used to keep the eyes wet. For any neuropathy associated with Sjogren's the treatment is by following guidelines in the CIDP section.

**Dermatomyositis & Polymyositis:** Dermatomyositis is an autoimmune disorder that consists of inflammatory myopathy and skin manifestations. Polymyositis is an autoimmune inflammatory myopathy without any skin involvement. The average age at diagnosis is 40, and is seen twice as commonly in women as compared to men. The average age of onset in childhood dermatomyositis is between five and 12 years. The younger individuals show a better prognosis.

Individuals with dermatomyositis present with many systemic symptoms. The most common are proximal muscle weakness, difficulty speaking (dysphonia) or difficulty eating (dysphagia). Associated with shortness of breath, visual changes, abdominal pain and internal malignancy (small cell cancer can be present in dermatomyositis).

The autoimmune attack targets the muscles; there is loss of muscle fibers in the hips and shoulders. People have difficulty getting out of the chair and difficulty holding their arms above the head. Women notice they cannot comb their hair. Children, who previously could jump up from the floor, will use their hands to get up from the floor and use their hands by keeping them on the knees to push them up in a standing posture called (Gowers Sign).

**Dermatomyositis skin signs:**

- **Gottron's papules**, raised reddish skin lesions over the fingers, elbow or knee
- **Gottron's sign**, little spots or blemishes reddish, over fingers, elbow, knees
- **Mechanic's hand**, fissured, scaly hands with peeling skin.
- **Periungual telangiectasia** Small tiny blue or red blood vessels show up around the skin of the finger surrounding the nail
- **Shawl sign** reddish spots slightly raised distributed in a "shawl" pattern over the shoulders, arms and upper back.
- **Proximal Weakness**, difficulty raising arms up and difficulty raising knees while sitting in a chair.

Polymyositis individuals just present with weakness and do not have any skin findings.

## Diagnosis

- Neck flexor weakness (tested by placing the hand on the forehead and weakness can be seen as the person cannot move the head forward) along with weakness in elevating arms above shoulders or difficulty in getting out of a chair, it's called proximal weakness. Abnormal laboratory tests include elevated E.S.R., ANA can be positive CPK and LDH are usually elevated. Dermatomyositis individuals need chest X-ray to rule out malignancy along with stool guaiac (blood test in stools at least three samples to check for malignancy). Polymyositis individuals do not need any tests for malignancy.
- The muscle enzymes are usually elevated (CPK, LDH). We do recommend a muscle biopsy we have found this to be reported normal in spite of the individual having clinical Myopathy.
- Muscle Biopsy is usually diagnostic. It shows inflammation lots of white blood cells accompanied by muscle fibers showing atrophy in some areas. This is a classic finding in any autoimmune diseases. You will see some normal cells, some inflammation and some atrophic cells. (Biopsy should be done before the EMG test).
- EMG/NCV shows a myopathy pattern. Myopathic short duration, low-amplitude polyphasic units on voluntary activation appearance of small amplitudes polyphasic waves, there is rapid recruitment of motor units and complete interference pattern of reduced amplitude on weak effort. Increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves;

## Treatment:

- Both conditions response to prednisone at a dose of 2mg/kg and this confirms the inflammatory myopathy. Case reports have shown that alcohol, and statins may cause the above syndromes. Other drug induced causes are penicillamine, nonsteroidal anti-inflammatory agents (nifluric acid and phenylbutazone), hydroxyurea (Hydrea), pravastatin (Pravachol), clofibrate (Atromid-S) and ipecac. Removal of the offending drugs will reverse the myopathy.
- Many studies have shown a benefit of low dose **Minocin 100 mg** taken on alternate days three times a week. Minocin needs to be taken for several months before a benefit is seen. Complete remission of all symptoms is obtained in most individuals with Minocin. **Please see full protocol under Rheumatoid arthritis** section.
- Magnesium supplements at 400mg two or three times a day help with the inflammation.
- Short term use of steroids is helpful in majority of the individuals. For the full protocol on immune modulator treatment look under CIDP treatment guidelines in the neurology chapter. Steroids are not recommended for long term therapy as they will cause proximal muscle weakness in the long run. I.V.I.G. is a better drug to give at the start of the disease and provides long term remission the recommended dose is 2g/kg in five divided doses daily for five days. In older individuals it should be given on alternate days. If the individual has a high myoglobin levels or high creatinine IVIg should be held as this can predispose to renal failure. If an older individual develops renal failure then immediate dialysis is recommended to reverse this condition.
- If the individual does not improve with anti-inflammatory treatment then they need to be on a Gluten free diet. Which is they only eat Fruits, vegetables, Milk products, Fish, chicken and Beef. No Wheat, Rye or Barley and oats. Creatinine supplements are helpful if the individuals have muscle atrophy.

**Systemic Lupus Erythematosus** is a chronic (long-lasting) autoimmune disease which affects joints, muscles and nearly every part of the body. SLE is the single biggest killer of women all over the world. Sharing a bedroom during childhood was associated with a higher risk of developing lupus in a study. A record of diarrhea type illness, rubella or mumps during the first year of life was also significantly associated with developing SLE later in life. The infections linked with SLE are, Hepatitis-C virus (HCV) infection, Herpes-Zoster, Epstein-Barr virus and cytomegalovirus (CMV). New attacks of SLE are associated with exposure to these viruses.

Drug-induced lupus is a syndrome which shares characteristics with autoimmune lupus erythematosus (SLE). Some of the drugs which can trigger SLE are minocycline, statins, anti-TNF-alpha agents, sulfadiazine, hydralazine, chlorpromazine, isoniazid, methyldopa, penicillamine, quinidine, beta blockers and anti anticonvulsants. The syndrome is characterised by arthralgia, myalgia, pleurisy, rash and fever in association with antinuclear antibodies in the serum. The recognition of drug-induced lupus is important because it reverses within a few weeks of stopping the inducing drug.

SLE individuals usually have a butterfly shaped rash over the cheeks and across the bridge of the nose. Some common symptoms of SLE are as follows.

### **Symptoms**

- Discoid Skin rash (scaly, disk-shaped sores on the face, neck or chest)
- Sensitivity to sunlight, at times so severe they cannot tolerate the sun.
- Arthritis (pain, stiffness in joints) Fever, Anemia , Fatigue , Muscle aches
- Serositis (inflamed lining around the heart, lungs, & abdomen, causing pain and shortness of breath)
- Kidney failure (protein leak) , Hypertension
- Seizures, strokes, confusion, Ulcers in the mouth.
- Immune deficiency (risk of infection)
  
- Nausea ,Vomiting and diarrhea , Lack of appetite, Weight loss
- Sensitivity to cold (Raynaud's phenomenon) associated with CMV infection.

### **Tests:**

- A sedimentation rate (ESR) or C-reactive protein (CRP) are elevated.
- A urine analysis to detect kidney problems shows elevated protein.
- Chest X-rays may be taken to detect lung damage.
- An EKG to detect heart problems.
- ANA antibody may be positive.(even the lowest titer is considered positive)
- Anti Hepatitis C antibody may be present.
- IgG level & IgG subclass levels may be low showing immune deficiency.

### **Treatment Options:**

- If Hepatitis-C antibody is found then a combination therapy with, pegylated interferon and ribavirin is given. Prednisone and immunosuppressive drugs are primary treatment of SLE, for the complete management of immunosuppressive drugs please check treatment guidelines under the CIDP section. IVIg is very effective treatment for SLE. If a deficiency of IgG or IgG subclass are seen then treat the immune deficiency with IVIg. Antibodies against all the viral infections are contained in IVIg including varicella zoster. If Varicella Zoster immune globulin is not available IVIG can be used in its place.
- Immunosuppression with SLE can be accompanied by emergence of viral infections. There are many viruses associated with SLE, antiviral antibodies can be tested against all of them. If an individual is having recurrent attacks then consideration should be given to treat the appropriate virus. Here are the available treatments. Chemoprophylactic regimens for cytomegalovirus (CMV), Epstein-Barr virus, herpes simplex have included oral acyclovir, intravenous and oral ganciclovir, famciclovir, valganciclovir and valacyclovir. People with primary varicella-zoster virus (VZV) can receive VZV immune globulin after contact with either varicella or zoster. With treatment the prognosis is good and long term survival reported.

**Antiphospholipid Syndrome (APS):** Antiphospholipid syndrome, also known as Hughes syndrome, is an autoimmune disorder characterized by elevated levels of multiple antibodies (Y shaped proteins) that are associated with blood clots in veins and arteries. This condition is well known for causing an easily treatable infertility syndrome. It is also associated with multiple complications of pregnancy including poor fetal growth. In young people it is considered a common cause of heart attacks and strokes. Celiac disease can be present in many individuals with APS syndrome.

Lupus anticoagulant (LAC) and anticardiolipin antibody (aPL) and antibodies that are associated with APS Syndrome. In one study 85 % of APS individuals had chronic active gastritis. After helicobacter pylori eradication, disappearance of antiphospholipid antibodies syndrome has been reported. Another study reported showed eradication of helicobacter pylori led to disappearance of ACA, LAC antibodies in 84 children.

**APS can present as:**

- **Vascular thrombosis** (blood clot involving artery or vein)
- **Embolism** (blood clot that travels and occludes a distant blood vessel)
- **Infertility** (or as recurrent pregnancy loss).
- **Thrombocytopenia** (a low platelet count),
- **Pulmonary hypertension** (high blood pressure in the arteries that supply the lungs)
- **Sensorineural hearing loss** This is sometimes also called "nerve deafness"
- **Brief stroke-like episodes** transient weakness, numbness or loss of vision
- **Heart valve problems**, sometimes requiring valve surgery or valve replacement
- **Skin rash** Persistent or transient blotchy, lacy bluish rash (called livedo reticularis)
- **Skin ulcers**, commonly on the legs or feet due to occlusion of small blood vessels.



- **“Catastrophic” APS** – a life-threatening condition in which clots form in small blood vessels involving heart, lungs, brain, kidneys and causing them to dysfunction.
- **Seizures, Epilepsy & Stroke.**

#### **Conditions associated with APS include:**

- **Systemic Vascular Thrombosis:** While the deep veins of the legs are the most frequent sites of blood clots, these clots can break loose and form smaller clots, which can travel and involve virtually any vein or artery. Any individual presenting with thrombosis should be suspected for APS.
- **Pregnancy Loss and Other Complications:** APS is associated with infertility and recurrent miscarriages. Most studies have estimated 20-percent of pregnant women have aPL antibodies; most of these women do not have any signs or symptoms. Some women have recurrent (two or more) pregnancy losses. Pregnancies occurring in women with APS are at increased risk of miscarriage, prematurity, of the fetus, and preeclampsia (high blood pressure during pregnancy). Pregnant women with APS are also more prone to develop deep vein thrombosis during the period between childbirth and the return of the uterus to its normal size.
- **Skin Disorders:** Skin conditions with include APS are livedo reticularis (mottled discoloration of the skin), ulcers on the skin, usually on the legs, and sometimes skin necrosis (black areas of skin after tissue dies).
- **Seizures, Stroke and TIA, neuropathy:** Stroke is associated with APS, (blood clotting a vessel of the brain). Multiple strokes can sometimes lead to a condition called multi-infarct dementia. Transient ischemic Attacks (TIA) are mini strokes from which the individual recovers fully within 24 hours. Multiple TIA can be seen in some individuals. Seizures, chorea (uncontrolled dancing hand or arm movements), migraines, Guillain-Barré syndrome, neuropathy, transverse myelitis (a disorder caused by inflammation across the spinal cord), and conditions similar to multiple sclerosis have been seen in APS.
- **Heart Valve Disease:** Heart valve disease called Libman-Sacks endocarditis is sometimes seen in individuals with aPL antibodies. In this condition, growths on the heart valve can break off and travel through the blood stream, causing embolic events.
- **Lupus and Other Autoimmune Disorders:** APS has also been associated with other autoimmune disorders, including myasthenia gravis, Graves' disease, autoimmune hemolytic anemia, Lupus (SLE).

**Diagnosis:** APS is diagnosed if a person experiences one or more episodes of thrombosis or pregnancy loss. Laboratory diagnosis of APS relies on the demonstration of positive antiphospholipid antibodies (aPL) and the lupus anticoagulant (LA)  
Anti H.Pylori antibodies need to be checked in the individual.

#### **Treatment for APS**

- In general, for a person who has aPL antibodies and a thrombotic event, a short-term course of **heparin** (an anticoagulant, which is a type of medication used to

prevent blood clots from forming or getting bigger) is followed by long-term sometimes life-long treatment with **aspirin** 80 mg tablet taken daily.

- **Antibiotics: We recommend using typical 2 wk anti-H.Pylori therapy including omeprazole (20 mg bd.), clarithromycin (500 mg bd.) and metronidazole (500 mg bd.)**
- In women with moderate to high levels of aPL antibodies and a history of pregnancy loss who wish to get pregnant again. Aspirin alone can work in 70% of these individuals. It is recommended that once the individual gets pregnant they are also started on heparin 1000 units subcutaneously daily.
- Some of these individuals will not respond to aspirin or heparin and will require other treatments. If IVIg is available then IVIg can be used 400mg/kg every four weeks to help a individual get pregnant. It can be continued thorough the pregnancy.
- Steroid and cyclophosphamide pulses are used in all cases with neurological, cardiac and abdominal diseases. Please see the individual diseases and list of all the drugs that can be used in the CIDP treatment section.

**Fibromyalgia:** Fibromyalgia syndrome (FMS) is a rheumatologic condition characterized by spontaneous, widespread soft tissue pain, sleep disturbance, fatigue and extensively distributed areas of tenderness known as tender points. FMS is an autoimmune condition; recently a study reported antibodies to serotonin receptors in FMS. Gangliosides and phospholipids antibodies are also found in about 70% of the individuals with FMS. Other autoimmune diseases are usually associated with FMS. Frequent remissions and relapses are seen in FMS, the disease targets mainly women. Almost all the People with PTSD (post traumatic stress disorder) have fibromyalgia. People with fibromyalgia have alterations in sleep pattern and changes in neuroendocrine transmitters such as serotonin, substance P, growth hormone and cortisol, along with dysregulation of the autonomic nervous system.

Symptoms of fibromyalgia may be created by poor sleep. The brainwave recordings in fibromyalgia individuals in sleep, show disturbance of the non-REM (non-rapid eye movement) sleep phase, due to intrusions of alpha waves with infrequent progression to deeper stages of sleep. The alpha waves are only present when a person is awake and eyes are closed. As soon as the eyes open alpha disappears. These findings correlate with individual reports of awakening repeatedly and having unrefreshed sleep. Release of growth hormone occurs primarily during stages 3 and 4 of sleep. Individuals with fibromyalgia have low insulin growth factor (IGF) levels, an indication of low growth hormone secretion. During the night our bodies produce melatonin which helps the body relax. Higher levels of melatonin cause inflammation, this type of sleep related inflammation is seen in many autoimmune including Fibromyalgia. FMS and rheumatic arthritis individuals, wake up with stiffness and pain, caused by increased melatonin production during sleep.

The pineal gland produces melatonin at night and produces histamine during the sunlight hours to help keep us active. In comparison the mouse pineal is exactly opposite and

produces histamine during the night to help the mouse stay active in darkness. Humans by creation are not suited for work during the dark hours.

Mycoplasma and Lyme infections are frequently reported in Fibromyalgia individuals and may be an important cause of this disease. Recent reports show a higher rate of fibromyalgia in breast implant recipients.

**Fibromyalgia symptoms:** Stress will usually trigger neck pain, sleep becomes disturbed early. The attacks of numbness start on left or right side of the body. Attacks of diarrhea and constipation may start in some people. Pain may shift from one area to another, can be present all over the body. Pain and stiffness are worse in the morning and as the day goes by stiffness and pain become less. Individuals have tender points in their neck, shoulders, elbows, chest, hips, knees and ankles. Touching the tender points causes pain. Individuals complain of “knots” in the neck and back, they hear grinding sounds and assume their bones are cracking. The sound is actually caused by tight muscle fibers, as they are stretched. Poor sleep is common, and the person wakes up tired. They complain that they have the feeling of being run over by a truck. Fibromyalgia and Chronic Fatigue are overlapping conditions so please review both disorders.

**Diagnosis:** Fibromyalgia is easily diagnosed by history alone. The only examination needed is of tender points. No blood tests are needed or x-rays are required for the diagnosis. A diagnostic criterion has been made by the American academy of Rheumatology but they have specified it should only be used for research purposes.

**Treatment:**

- We recommend a two week trial of doxycycline 200 mg in all individuals with Fibromyalgia. If this trial is of benefit then it can be repeated in responders. This is advised due to large number of individuals being tested positive with Chlamydia pneumonia.
- Supplement of **magnesium** will help with the pain and the individuals sleep better, dose 400 mg twice a day or just eat the leafy green vegetables rich in magnesium. Biological clock and magnesium status are linked. Central magnesium regulation controls the suprachiasmatic nuclei and of pineal gland, which makes melatonin.
- **DHEA:** Supplement is better for those individuals who have low cortisol, should be taken early in the morning before getting out of bed. Women need to watch out for the associated short temper they will get. It tightens up the skin and makes the muscles stronger.
- **Vitamin B-12** sublingual supplements are effective in reducing pain and improving brain functions.
- **Exercise.** Aerobic and strength-training activities have been associated with significant improvements in FMS. Stretching three to four times a day with brisk walking also helps.
- **Acupuncture.** Acupuncture is an extremely useful analgesic treatment for FMS.
- **Hypnosis.** hypnosis improved functioning and reduced pain more than physical therapy
- Hyperbaric oxygen (HBO) therapy is effective in fibromyalgia..

- Drinking **warm** full 100% milk at night increase tryptophan and serotonin at night for a better sleep. Warming of the milk activates tryptophan in the milk. Tryptophan supplements in the body are converted to serotonin. This takes care of the depression. Those countries where Tryptophan is available as a supplement can try this in place of milk.
- Pregabalin at 300 and 450 mg/day was associated with significant improvements in sleep quality, fatigue, and global measures of change in FMS
- Please see the muscle stiffness chapter at the end of this book.
- Colostrum will also help in fibromyalgia as it provides IgG.

**Chronic Fatigue Syndrome / Gulf war syndrome (GWS):** Chronic Fatigue syndrome (CFS), FMS (fibromyalgia) and Gulf war syndrome are inter-related. We find they are just different expressions of the same problem. In chronic fatigue the main symptom is tiredness, which does not go away with normal sleep. We have discussed how elevated melatonin keeps these individuals awake discussed in the FMS chapter above. In all humans a good night sleep should make them fresh again, this does not happen in CFS/FMS/GWS. Individuals with CFS have frequent infections, they can be viral or bacterial, most common reported pathogen is Mycoplasma. Chronic fatigue syndrome can result from diverse causes which include exposure to toxins, pesticides, infections and every individual needs a tailor made workup. There are several immunological abnormalities reported in CFS, along with hormonal disturbances specially reduced production of cortisol. In a recent insecticide exposure 26 women developed fibromyalgia and chronic fatigue which caused long term disability. The pain component in these disorders is due to FMS.

**Symptoms: Fatigue,** tiredness no energy which is present even after a good night rest.

- Short-term memory loss or concentration problems
- Sore throat, frequent infections, night sweats, fever
- Multi-joint pain without joint swelling or redness
- Bowel disorders , constipation, diarrhea
- Headaches, Brain fog, Muscle pain
- Non-refreshing sleep, dry eyes, Increased thirst
- Post-exertional malaise lasting more than 24 hour, shortness of breath
- Lymph nodes palpable

**Tests:**

- Hormonal test. Check TSH, T3, T4, antithyroid antibodies, morning cortisol levels.
- Infections: antibodies against Cyto Megalo Virus, Epstein Barr virus, Human Herpes Virus 6, Chlamydia, H.-Pylori, Borrelia, Candida and Amoebae, Mycoplasma
- Immunological: IgG levels and IgG subclass levels.
- General Tests: CBC, CRP, B12 , B6 , Magnesium

**Treatment:**

- If any Hormonal or vitamin deficiency is found the specific deficiency needs to be treated. If B-12 deficiency is found automatically give h-pylori prophylaxis treatment as shown in the gastric section.
- If the IgG levels or IgG-subclass levels are low then treatment with IVIg should be given. If IVIg is not available use colostrum supplement look at the end of this book in the colostrum section.
- If Borrelia or Chlamydia antibodies are present then give 200 mg Doxycycline daily for two weeks. (We recommend this antibiotic for all individuals) Dietary guidelines in the diet section should be followed.
- Some of the Gulf War veterans have been exposed to depleted uranium which result in Lymphoma or leukemia this would need appropriate treatment in a cancer center. Please see the Lymphoma section.

**Mixed Connective Tissue Disease (MCTD) & UCTD (undefined connective tissue disease):** These diseases are called ‘overlap-syndromes’. Individuals with MCTD have symptoms of lupus, scleroderma, myositis and rheumatoid arthritis, appearing together with antibodies against one specific antigen, namely RNP (ribonuclear protein antibody). It is thought to be a distinct disease entity and called MCTD. Polyvinylchloride (PVC) Exposure is associated with MCTD. Sjogrens syndrome is very common in MCTD. The prognosis is favorable if the disease is adequately treated. There is a tendency for MCTD to evolve into SLE or systemic sclerosis. In the last stages of MCTD development of pulmonary hypertension, scleroderma or renal crisis can result in death. At times the individuals symptoms may not be well defined. That is why the term UCTD (undefined connective tissue disease) is used. Commonly Raynauds phenomenon, joint pains, arthritis and muscle pains symptoms are usually present. The evolution is very diverse, some individuals remain in early phase and never progress while others evolve quickly into a real form of lupus or another type of connective tissue disease.

#### **Symptoms of MCTD:**

**Trigeminal Neuralgia:** Attacks of pain in the face or jaw are usually the first symptoms of MCTD syndrome.

**Sjogrens syndrome:** Mucous membranes of skin (mouth, vagina) and the eyes may be dry due to the Sjogrens Syndrome.

**Raynaud’s phenomenon :** ( hands feet and nose can become painful on exposure to cold).

**Swollen fingers** (due to mild arthritis)

**Sclerodactyly** (thin fingers with hard tight skin and limited mobility).

**Myositis** (inflammation of muscles causing shoulder, arm and hip weakness)

**Lungs:** (shortness of breath)

**Esophagus** (difficulty in swallowing)

**Heart inflammation** of hearts outer covering layer called pericardium causes (pericarditis) may be acute. The heart muscle itself gets inflamed resulting in (myocarditis), which may cause heart failure or arrhythmia.

**Neurological,** aseptic meningitis (inflammation of the brain without an infection), headache, seizures, psychosis, encephalopathy, transverse myelitis, ataxia, aseptic

meningitis, blindness, trigeminal sensory neuropathy, polyneuropathy and entrapment neuropathy seizure and gait disturbance , reversible dementia, psychological issues, facial nerves paralysis is seen.

**Renal** involvement is rare (especially damage to the renal blood vessels) as well as (damage to the renal filtering units).

**Arthritis:** multiple joints can have arthritis.

**Diagnosis of MCTD:** The diagnosis is based on complaints, symptoms and organ involvement and on the presence of **anti-RNP antibodies**. This is the only connective tissue disease for which one specific type of antibody is necessary to make a diagnosis anti-RNP antibody

**Treatment of MCTD:** Treatments with a low dose of corticosteroids have been successful, The treatment has to be individualized for each individual.

Please see the chapters of individual diseases for more information.

## Chapter 11 Psychiatric Autoimmune Disease

**Autism :** Autism consists of behavioral symptoms with dysfunction in social interaction and communication in affected children. It is typically associated with restrictive, repetitive, and stereotypic behavior and manifests within the first 3 years of life. Autism has multiple causes (etiologies) with both genetic and environmental, dietary contributions, which may explain the spectrum of behaviors seen in this disorder. One proposed etiology for autism is viral infection which can cause an autoimmune reaction. The mechanism, by which viral infection may lead to autism, be it through molecular mimicry of the central nervous system (CNS), through infection elsewhere in the body acting as a trigger for disease in the CNS. There have also been several studies reporting either gluten (in grain) or casein (in milk), or both casein and gluten can trigger the immune dysfunction. Autoantibodies (IgG) to **neuron-axon filament protein (NAFP)** and **glial fibrillary acidic protein (GFAP)** are significantly increased in autistic individuals. Studies showing elevated brain specific antibodies in autism support an autoimmune mechanism. Virus specific antibodies associated with measles virus have also been demonstrated in autistic subjects

There was a relationship between vaccination and Autism. Environmental exposure to mercury is believed to harm human health by modulation of immune homeostasis. A mercury link with the immune system had been postulated due to the involvement of postnatal exposure to thimerosal, a preservative added in the MMR vaccines. However those vaccines have been phased. Still there are reports that some children have higher mercury levels in their hair analysis. Mercury occurs naturally in the environment. According to FDA toxicologist, approximately 2,700 to 6,000 tons of mercury is released annually into the atmosphere naturally by degassing from the Earth's crust and oceans. Another 2,000 to 3,000 tons are released annually into the atmosphere by human activities, primarily from burning household and industrial wastes, and especially from fossil fuels

such as coal. A significant percentage of children with autism develop anti-SK (streptokinase), anti-gliadin and casein peptides and anti-ethyl mercury antibodies

Multiple case reports show an association between CMV and Autism. One individual with autism who also had (ALPS) was treated with steroids who made a good recovery. A report on two case of autism which developed at age 3 after a infection were treated with ACTH both individuals improved, and one of them who got ACTH soon after the infection had complete resolution of his symptoms. All children with autism demonstrate deficits in, social interaction, verbal and nonverbal communication, and repetitive behaviors or interests. In addition, they will often have unusual responses to sensory experiences, such as certain sounds or the way objects look. Each of these symptoms runs from mild to severe. The symptoms will present in each individual child differently. For instance, a child may have some trouble learning to read but exhibit extremely poor social interaction.

Some of the abnormalities seen in autism may be caused by chemicals like MSG, causing hyperstimulation of the glutamate receptors. Glutamate is the most abundant excitatory neurotransmitter in the nervous system. In excess, glutamate triggers a process called excitotoxicity, causing neuronal damage and eventual cell death. Microinjection of glutamate into neurons produces spontaneous seizure like activity. Many reports have shown increases of glutamate in blood and platelets of autistic subjects. Autopsy studies in subjects with autism have shown specific abnormalities in the glutamate receptors and glutamate transporters in the cerebellum. These abnormalities may be directly involved in the pathogenesis of Autism. Glutamate maintains its toxicity in animals even when administered orally. Males appear to be more sensitive than females to excitotoxins triggers. Excess excitotoxins cause an imbalance in the flow of calcium, which leads to activation of a complex inflammatory cascade, release of inflammatory mediators and ultimately causes the death of neurons.

#### **Symptoms of autism:**

- Problems developing nonverbal communication skills, such as eye-to-eye gazing, facial expressions, and body posture.
- Failure to establish friendships with children the same age.
- Lack of interest in sharing enjoyment, interests, or achievements with other people.
- Lack of feelings. People with autism may have difficulty understanding another person's feelings, such as pain or sorrow.

**Test:** Testing for food allergies needs to be done and if any allergies are found then they should be addressed. Testing for IgG and IgG subclass levels should be done. If low levels, of (IgG or IgG subclass) are found, then the child is considered suffering from a immune deficiency and treatment with IVIg may be required. All the individuals with autism should get a Gastro-intestinal evaluation to look for inflammation and antigliadin antibodies

should be checked. **E.E.G.** can be done to evaluate for epilepsy. **M.R.I.** scan of the head is done to evaluate the brain damage.

**Treatment recommendation:** Autistic children need to be placed on a special diet.

- The diet needs to be free of excitotoxins triggers from the diet. This simply involves reading labels and closely monitoring food and supplement intake to avoid excitotoxins. Excitotoxins are neurotransmitters such as glutamate or aspartate that can excite the nerves to death when their levels are not regulated properly. Foods or supplements that contain excitotoxins include MSG (monosodium glutamate), glutamic acid, glutamine, nutrasweet, aspartate, aspartame, and cysteine. Mercury and aluminum can also serve to trigger glutamate release. MSG is found in most of the food prepared by major fast-food chains.
- A diet free of Milk (casein) plus free of wheat, rye, barley, millet, oat (gluten). This diet should contain all the vegetables, corn, fruits, honey, rice, eggs, chicken, beef, fish and water. There is no ketchup in this diet if you want to then get the gluten free ketchup. Try your child on this for a month and if you see improvement then you can try to add milk products slowly. If the child cannot tolerate the products switch back to the Vegan diet. Conversely you need to try the gluten products and see if the child tolerates them. If they do then you will only need the milk free diet.
- Some children may have gastritis and food allergies thus evaluation should be undertaken if there is any evidence of an h pylori infection. If evidence found need to be treated. Gastritis responds to the use of colostrum and even by drinking IVIG in a cup orally.
- If exposure to and mercury is suspected then to remove this Chinese parsley (Cilantro) cilantro has been used. (Has been used by dentist successfully to remove mercury in the body from dental amalgam adult dose is 400mg bid)
- If the child has a history of exposure to an infection and symptoms developed after that then Adrenocorticotrophic hormone ACTH can be tried to reduce any autoimmune related inflammation.
- A supplement that some parents feel is beneficial for an autistic child is Vitamin B6, taken with magnesium (which makes the vitamin effective). The result of research studies is mixed; some children respond positively, some not at all or very little.
- Behavior therapy is recommended in all cases.
- If IgG or IgG-subclass levels are low consider IVIg treatment. Low levels mean the person has immune deficiency. Those who cannot get IVIg can try colostrum.



From our analysis molecular mimicry plays an important role in Autism and a new case should be treated with immunomodulation and removal of the offending cause if possible. For epilepsy treatment please see the neurology section.

**P.A.N.D.A.S.** (N.I.H. guidelines) Obsessive compulsive disorder and other behavior disorder in children can be a autoimmune reaction triggered by streptococcal infections and have been called, **P**ediatric **A**utoimmune **N**europsychiatry **D**isorders **A**ssociated with **S**treptococcal infections. These are essentially autoimmune disorders and treated with anti inflammatory medicines. According to the NIH following guidelines have been issued for their diagnosis.

**Diagnosis** of PANDAS is a clinical diagnosis, which means that there are no lab tests. Instead clinicians use 5 diagnostic criteria for the diagnosis of PANDAS

- Presence of Obsessive-compulsive disorder and /or a tic disorder
- Childhood onset of symptoms (age 3 years to puberty)
- Symptoms which are Waxing & Waning
- Association with group A Beta-hemolytic streptococcal infection (a positive throat culture for strep. or history of Scarlet Fever.)
- Association with neurological abnormalities (motor hyperactivity, or adventitious movements, such as chore form movements).

Like any other autoimmune disorder the symptoms are waxing & waning like the stock market. Children with PANDAS seem to have dramatic ups and downs in their OCD and/or tic severity. Tics or OCD which are almost always present at a relatively consistent level do not represent an episodic course. Many kids with OCD or tics have good days and bad days, or even good weeks and bad weeks. However, individuals with PANDAS have a very sudden onset or worsening of their symptoms, followed by a slow, gradual improvement. If they get another streptococcal infection, their symptoms suddenly worsen again. The increased symptom severity usually persists for several weeks, but can last for several months or longer. Children with PANDAS often experience one or more of the following symptoms in conjunction with their OCD and/or tics:

- ADHD symptoms (hyperactivity, inattention, fidgety)
- Separation anxiety (Child is, clingy and has difficulty separating from the caregivers. For example, the child may not want to be in a different room in the house from the parents.)
- Mood changes (irritability, sadness, emotional liability)
- Sleep disturbance, Joint pains
- Night- time bed wetting and/or day- time urinary frequency

- Fine/gross motor changes (e.g. changes in handwriting)

**Test:** for PANDAS: ASO (anti-streptococcal antibody) titer, which rises 3-6 weeks after a strep. Infection will be elevated in children with PANDAS. It is important to note that some grade-school aged children have chronically “elevated” titers. These may actually be in the normal range for that child, as there is a lot of individual variability in titer values. Because of this variability, doctors will often draw a titer when the child is sick, or shortly thereafter, and then draw another titer several weeks later to see if the titer is “rising” – if so, this is strong evidence that the illness was due to strep. (Of course, a less expensive way to make this determination is to take a throat culture at the time that the child is ill.)

**Treatment of PANDAS:** Penicillin and other antibiotics kill streptococcus and other types of bacteria. The antibiotics treat the sore throat or pharyngitis caused by the streptococcus. In PANDAS, the antibodies produced by the body in response to the streptococcus are the cause of the problem, not the bacteria themselves. The results of a controlled trial of plasma exchange (also known as plasmapheresis) and immunoglobulin (IVIG) for the treatment of children in the PANDAS subgroup was published in *The Lancet*, Vol. 354, October 2, 1999. All of the children participating in the study had clear evidence of a strep. Infection as the trigger of their OCD and tics, and all were severely ill at the time of treatment. The study showed that plasma exchange and IVIG were both effective for the treatment of severe, streptococcus triggered OCD and tics, and that there were persistent benefits of the interventions.

### **Neuropsychiatric autoimmune syndromes & Autoimmune Depression:**

Depression is one of the more common symptoms of autoimmune diseases, and commonly missed, diagnoses by the general practitioner today. While an otherwise healthy individual can suddenly present with symptoms of primary depression, confusion, hallucinations, suicide attempts is difficult to understand. Though this is happening in quite a few medical individuals, but most of them are not being diagnosed as having an underlying autoimmune problem. We propose that sudden psychiatric outbursts, suicides are the result of autoimmune disease. A quick diagnosis anti-inflammatory treatment can avoid hospitalizations and improve the persons quality of life. Instead of usual psychiatric medications, immune modulators are better suited for these individuals. Autoimmune disorders in general and SLE and primary Sjogrens in specific are potential causes of psychiatric manifestations.

Here is a case study of a young man who was admitted in the hospital for agitation. During the hospital stay he had auditory hallucinations and felt persecuted. He received antidepressant and the condition remitted in a few days. He was discharged, a few months later he was readmitted for agitation. He became calm quickly and was discharged home. A few months later, he was found in a coma, and admitted to the hospital. The spinal tap revealed blood cells. C.T scan of the head showed fresh blood within the spinal fluid. The

diagnosis of cerebral bleeding due to vasculitis was made. After regaining consciousness, the individual complained of reduced vision. This was believed secondary to inflammation in the nerve going to the eye, and the individual's vision improved with prednisone. He was sent home after he was able to walk. He was admitted again with suicidal ideas, his mood improved progressively with antidepressant treatment. Later this individual started having memory problems and disorientation. Signs of confusion rapidly disappeared without treatment. His mood felt better after starting fluoxetine (Prozac) 40 mg/day. After being hospitalized for four occasions in one year, the diagnosis of his systemic disease was revised by a rheumatologist. The individual was diagnosed to be suffering from Systemic Lupus Erythematosus associated with secondary Sjogren's syndrome. He received cyclophosphamide 2 gram intravenously per monthly six times. His vision improved, ocular dryness resolved, mood was stable and he did not suffer from hallucinations or delusion since. (This is a true story reported in the medical literature). There are many individuals like this who still get treated by routine antidepressants. They keep returning to neurological and psychiatric facilities, some commit suicide and few if ever get diagnosed as having an autoimmune disease.

American College of Rheumatology has developed nomenclature and case definitions for neuropsychiatric lupus syndromes. The time has come to extend these guidelines to nearly all autoimmune disorders which can present with depression. This depression has a tendency to cycle and is accompanied by remissions and relapses. Undiagnosed individuals can suddenly commit suicide. The autoimmune depression is commonly seen in women after childbirth.

**Tests:** MRI scan for new brain lesions, EEG to check for epilepsy, Sedimentation rate and CRP are elevated. Antibodies like anticardiolipin and ANA are present. Complement levels are lower. B-12 levels, Thiamine levels and B-6 levels need to be checked as autoimmune gastric disease may also cause vitamin B-12 deficiency.

**Symptoms:** Individuals present with headaches, mood disorders, confusion, anxiety, strokes, visual disorders and memory dysfunction. Seizures and weakness, numbness occurred only in SLE individuals.

**Treatment:** Prescription of corticosteroids or immunosuppressive drugs and specific antidepressant drugs, making sure to avoid lupus-inducing drugs in SLE and drugs with anticholinergic side effects which can make the eyes and mouth dry in Sjogren's syndrome. For the whole list of medications effective in autoimmune disorders please see list A under CIDP treatment.

**Post-traumatic stress disorder (PTSD):** PTSD is not known to be an autoimmune disorder yet. For the first time we present our findings to show it is an autoimmune disorder. PTSD is associated with other autoimmune diseases and tends to occur more frequently in women. PTSD is a debilitating condition that can develop following a terrifying event. People with PTSD have persistent frightening thoughts and memories of their ordeal and feel emotionally numb, especially towards people they were once close to. PTSD was first brought to public attention by war veterans, but it can result from any number of traumatic incidents. These include violent attacks such as mugging, rape, or torture; being kidnapped or held captive; child abuse; serious accidents such as car or train wrecks; and natural disasters such as floods or earthquakes. The event that triggers PTSD may be something

that threatened the person's life or the life of someone close to him or her. PTSD also develops in innocent bystanders and rescue workers, such as massive death and destruction after a building is bombed or a plane crashes. It has been seen in individuals undergoing complex surgery.

There is evidence that a part of the brain called amygdala-hippocampal region is involved in causing PTSD. The removal of this region and the resulting disconnection between right and left amygdala-hippocampal areas results in chronic PTSD symptoms. Smaller hippocampal volume has been reported in PTSD individuals and this does not return to normal size in long term studies. Studies have shown elevated levels of CRP an inflammatory marker in people with PTSD. In other studies Interleukin-6 (IL-6). Which is released by inflammatory cells and is a mediator of bone resorption was found to be elevated in the saliva of people suffering from PTSD. Anaerobic bacteria are more frequently seen in individuals with PTSD.

People with PTSD have sudden blackouts, attacks of rage during which they have assaulted other individuals without any recollection of events later on. These attacks are most likely epileptic seizures. Thought studies done in PTSD individuals to check for epilepsy they have been inconclusive, however many case reports have reported epilepsy in PTSD individuals. Some have related epilepsy due to increased use of alcohol. The studies done used peripheral electrodes to monitor seizures. Peripheral electrodes will not demonstrate deep hippocampal seizures. **The loss of hippocampal cells seen in PTSD is probably due to inflammation and epilepsy.**

In pre-surgical heart patients a dose of steroids was given before surgery and no symptoms of PTSD were seen in the patients getting steroids. We think that use of steroids would benefit the people suffering from PTSD. As PTSD is associated with a high mortality and development of other autoimmune diseases, these individuals need anti-inflammatory treatment. Blackouts reported by individuals should be investigated in epilepsy centers and appropriately treated. Please see the epilepsy section for management of seizures under inflammatory conditions. PTSD needs to be managed like an autoimmune disorder.

## **Chapter 13 Autoimmune Gastrointestinal Disorders**

**Celiac disease:** Celiac disease (CD) is an autoimmune gastrointestinal disorder. A condition manifesting in genetically predisposed individuals after exposure to wheat gluten. CD is characterized by inflammation, leading to injury to the cells lining the small intestine. The inflammation occurs due to molecular mimicry to gliadin, a protein found in such gluten-containing foods as **wheat**, rye, millet, oats and barley. Once gluten containing food is ingested by genetically susceptible individuals, immune attack against the cells called Villi is triggered resulting in destruction of Villi. The mucosal damage and subsequent malabsorption of nutrients leads to symptoms of weakness, infertility, neuropathy with anorexia, bloating, constipation, and diarrhea. It is estimated that more than

2 million people in the United States have celiac disease statistically, celiac disease is on the rise in the United States.

Gluten is a protein found in wheat, rye, oats, millet and barley. CD may be associated with neurological disorders, and the prevalence of epilepsy is higher in individuals with CD. The antigliadin antibodies frequently found in CD individuals are (antigliadin-A and antigliadin G antibodies respectively). Celiac disease is very damaging to the small intestine and can create many other problems, such as electrolyte imbalances, cardiac arrhythmias, villus atrophy, and short stature because of the diminished ability to properly absorb nutrients

**Symptoms and Observations in Celiac disease:** Common signs and symptoms of celiac disease include fatigue, abdominal pain, anemia, joint pains, bloating, constipation, diarrhea, infertility, tingling- numbness, and weight loss. The symptoms of CD can vary with each individual the only treatment for individuals with celiac disease remains a gluten-free diet. Some people may have no symptoms.

- White matter lesions in the brain, which can cause epilepsy, cerebellar ataxia(difficulty in maintaining balance)
- Cerebral occipital calcifications and epilepsy
- Selective IgA deficiency, (Immunoglobulin A deficiency)
- Constipation or diarrhea, pale foul-smelling, fatty stool, abdominal bloating
- Weight loss or weight gain, Fatigue tired all the time.
- Unexplained anemia -(a low count of red blood cells causing fatigue)
- Bone or joint pain, muscle cramps, Osteoporosis, osteopenia – weak bones
- Cardiomyopathy- enlarged heart
- Behavioral changes- short temper (Psychiatric)
- Swollen lymph nodes around the intestines and Lymphoma
- Tingling numbness in the legs (from nerve damage) Neuropathy
- Iron deficiency anemias due to reduced absorption of iron
- Missed menstrual periods (often because of excessive weight loss)
- **Infertility**, recurrent miscarriage
- Short Stature, cannot gain weight in infants and children.
- Pale sores inside the mouth, called aphthous ulcers
- Tooth discoloration or loss of enamel
- Itchy skin rash called dermatitis herpetiformis
- Hepatitis (inflammation of the Liver)
- Eyelid drooping, and (Holmes-Adie syndrome) see in neurology

Reactions to ingestion of gluten can be immediate, or delayed for weeks or even months. Some observations that demand attention in CD are,

- **Short stature** refers to being under-the-average height. Short stature results when childhood celiac disease prevents nutrient absorption during the years when nutrition is critical to a child's normal growth and development. Children who are diagnosed and treated before their growth stops may have a catch-up period

- **Complication Lymphoma and adenocarcinoma** are cancers that can develop in the intestine.
- **Osteoporosis** is a condition in which the bones become weak, brittle, and prone to breaking. Poor calcium absorption contributes to osteoporosis.
- **Miscarriage and congenital malformation** of the baby, such as neural tube defects, are risks for pregnant women with untreated celiac disease because of nutrient absorption problems.
- **Higher incidence in Down syndrome.** (In a study of 55 individuals with Downs, 21 were found to have antigliadin IgG and IgA antibodies. Some also showed low albumin.)
- **Lactose Intolerance.**

Celiac disease can be confused with irritable bowel syndrome, iron-deficiency anemia caused by menstrual blood loss, Crohn's disease, diverticulitis, intestinal infections, and chronic fatigue syndrome. Since celiac disease is hereditary, family members, particularly first-degree relatives-meaning parents, siblings, or children of people who have been diagnosed-may wish to be tested for the disease. About 5 to 10 percent of an affected person's first-degree relatives will also have the disease. About 5 to 10 percent of people with type 1 diabetes will have biopsy-confirmed celiac disease and 5 to 10 percent of people with Down syndrome will be diagnosed with celiac disease.

**Tests:** The serum antigliadin antibodies can be tested. Additionally a biopsy of the small intestine can be done to evaluate for Villi atrophy. More than 90% of individuals with celiac disease have the human leukocyte antigen (HLA DR3), (HLA DQ2), and (HLA DQ8).

#### **Treatment:**

- Diet without Gluten (No Wheat, Rye, Barley, Millet, oats) "**Plain without additives**" **meat, fish, rice, fruits, milk, cheese, yogurt, eggs and vegetables** do not contain gluten, so people with celiac disease can eat as much of these foods as they like.
- Cookies, Pasta, cakes, crackers, canned food especially soups, ketchup, mustard and soy sauce contain Gluten check the labels.
- Minority of individuals who fail to respond to a gluten-free diet may require intervention with immunomodulating drugs.
- Many studies show that infections may cause Crohn's disease which can co exist with CD there are reports that antibiotics, particularly Cipro with or without metronidazole, can control ulcerative colitis and Crohn's disease in some individuals, a course of Cipro 500-mg twice a day for ten days and metronidazole 250-mg four times a day on alternate weeks for a month is helpful and check liver

tests monthly. Tell individuals to stop the metronidazole if they feel any strange nerve sensations.

- In some cases low doses prednisone at 40 mg can be used and tapered after two weeks to help reduce inflammation.
- Several case reports have shown infliximab being used to induce a remission in refractory individual's with CD. Azathioprine has been used to induce remission in individuals unresponsive to dietary treatment and sometimes steroids have been used.

**Autoimmune Pancreatitis:** The pancreas is a small gland (weighing less than 8oz) located close to the stomach. The pancreas is a unusual gland that has both endocrine and exocrine functions. Its endocrine function produces three hormones, insulin and glucagon, which control processing of sugars in the diet (carbohydrate metabolism or breakdown). This third hormone is called vasoactive intestinal polypeptide (VIP) which controls intestinal movements, too much of the VIP causes a watery diarrhea and dehydration. The pancreas' exocrine function produces digestive enzymes (trypsin, chymotrypsin, lipase, and amylase). These enzymes are passed into the duodenum through a channel called the pancreatic duct. In the duodenum, the enzymes begin the process of breaking down a variety of food components, proteins, fats, and starches.

Autoimmune pancreatitis (AIP) is an recently recognized benign condition with a presentation similar to pancreatic neoplasia but responds to corticosteroid therapy. This is a relatively new autoimmune disease and a very important one. Millions of dollars are spent on the treatment of this disorder and the individuals still fair poorly. It is sometimes associated with other autoimmune diseases or inflammatory lesions, although in some individuals, pancreatic and biliary involvement represent the only known disease process. Many individuals present with pancreatic masses clinically and radiographically simulating pancreatic carcinoma, and associated bile duct strictures.

AIP was first described by Yoshida in 1995. It is an autoimmune inflammatory process of the pancreas. Diagnosis of chronic pancreatitis, is characterized by the presence of auto-antibodies, usually antibodies against human carbonic anhydrase, an enzyme located in the pancreatic ductal epithelium, and lactoferrin are frequently present in the serum of individuals affected by AIP

Recent reports have shown an association of *Helicobacter pylori* (*H. pylori*) infection, a well known cause of gastric ulcer, has been associated, via molecular mimicry. Considering that *H. pylori* might trigger autoimmune reaction through induction of an inflammation leading to AIP.

In almost half the cases, autoimmune pancreatitis coexists with other autoimmune diseases such as Sjogren's syndrome, extrahepatic cholangitis, primary biliary cirrhosis, autoimmune hepatitis, gastric peptic ulceration, thyroiditis and orbital pseudotumors. Celiac disease can also cause an autoimmune pancreatitis which respond to dietary changes and steroids. The serum IgG4 determination provides a useful means of distinguishing autoimmune pancreatitis from other disorders of the pancreas or biliary tract. Again this

elevation will not be seen in all the cases of AP. There maybe some involvement of the liver and gallbladder due to mild inflammation in some cases.

**Symptoms:** Individuals usually present with a 3-4 month history of recurrent abdominal pain, jaundice and pain loss. There is Celiac and peripancreatic lymphadenopathy

**Tests:** Individuals have an elevated serum levels or abnormalities in following

- hypergammaglobulinemia, (High levels of IgG)
- high serum IgG subclass 4 levels (IgG4)
- Pancreatic enlargements on C.T scan of the abdomen and pseudocysts.
- pancreatic duct strictures on Endoscopic retrograde pancreatography (ERP)
- C-reactive protein (CRP ) is elevated
- Sedimentation rate elevated
- ANA usually positive ( can be negative)
- Lymphoplasmacytic sclerosing pancreatitis is autoimmune

**Treatment** in all cases of pancreatitis should **be treated with 50 mg of prednisone daily**. This should be tapered after a week to 40 mg daily and then tapered by 10 mg every month.

- Once the individual is treated with corticosteroids the elevated serum IgG4 level falls. Within two months of being on prednisone the individuals is usually back to normal.
- H-pylori prophylaxis should be given with antibiotics as mentioned under gastric ulcer treatments, for those individuals who are suspected H. Pylori carriers.
- After prednisone is stopped start a anti-inflammatory treatments like aspirin.
- For non-responders consider IVIg and prednisone or plasmapheresis
- In properly treated cases, surgery and surgical complications can be avoided.

**Crohn's disease:** Is a chronic, recurrent autoimmune inflammatory disease of the intestinal tract, affecting the ileum, which is the last portion of the small bowel (ileitis, regional enteritis), also involves the colon (Crohn's colitis). The condition begins as small, microscopic areas of inflammation which grows gradually. The lining of the bowel can then become ulcerated and the bowel wall thickened due to inflammation. Eventually, the bowel may become narrowed or obstructed. The bacteria that grow in the lower gut may, act to promote inflammation by molecular mimicry. The condition occurs in both sexes and among all age groups, although it most frequently begins in young people. Jewish people are at increased risk of developing Crohn's, while African Americans are at low risk, which indicates a genetic link in this disease. When the ileum (final section of the small intestine, near the appendix) is involved, recurrent pain may be experienced in the right lower abdomen. At times, the pain mimics acute appendicitis. When the colon is the site, diarrhea (sometimes bloody) may occur, along with fever and weight loss. Crohn's disease often affects the anal area where there may be a draining sinus tract called a fistula. The disease usually runs the usual remitting relapsing course.



Individuals may also develop Arthritis, eye and skin problems, and in rare instances chronic liver conditions may develop. In the long run some cancers may form.

**Tests:** X-rays of the small intestine and colon (obtained through an upper GI series and barium enema) are usually required. In addition, a visual examination (sigmoidoscopy) of the lining of the rectum and lower bowel is usually necessary. A more thorough exam of the entire colon (colonoscopy) is often the best way of diagnosing the problem

**Treatment:** In all individuals fasting on alternate days should be tried. They also need to be tried on celiac diet which consists of rice, fish, milk, fruits and vegetables. Increase fluid in the diet help eliminate the toxins.

- **Antibiotics** Since there is frequently a bacterial infection along with Crohn's disease, antibiotics are often used to treat this problem. Two that are commonly used are ciprofloxacin (Cipro 500 mg twice a day for two weeks) and metronidazole (Flagyl) 250 mg four times a day on alternate weeks for two weeks.
- **Cortisone or Steroids** Prednisone low dose can be used to control flare ups for a short time a dose of 40 mg is used at first and slowly tapered to 5 mg a day. A three week course is recommended.
- **Anti-inflammation drugs** Sulfasalazine (Azulfidine), a group of drugs called the 5-aminosalicylates. These drugs are most useful in maintaining a remission, once the disease is brought under control. They are most effective when the disease is present in the colon. These are available in oral and enema preparations.

For a complete list of drugs including IVIg which is very effective in treating inflammation please see the list of drugs under the CIDP treatment guidelines. **Imuran or Azathioprine should be avoided in Crohns individuals** as it is associated with a increased incidence of Pancreatitis.

**Ulcerative Colitis:** Ulcerative colitis is an autoimmune inflammatory bowel disease (IBD), the general name for diseases that cause inflammation in the small intestine and colon. It can be difficult to diagnose because its symptoms are similar to other intestinal disorders and to another type of IBD called Crohn's disease. Crohn's disease differs because it causes inflammation deeper within the intestinal wall and can occur in other parts of the digestive system including the small intestine, mouth, esophagus, and stomach. Ulcerative colitis can occur in people of any age; it affects men and women equally and appears to run in families, with reports of up to 20 percent of people with ulcerative colitis having a family member or relative with ulcerative colitis or Crohn's disease. A higher incidence of ulcerative colitis is seen in Whites and people of Jewish descent. It is associated with bacteria called *Fusobacterium varium*.

**Symptoms** of ulcerative colitis: The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea. Individuals also may experience anemia, fatigue, weight loss, loss of appetite, rectal bleeding, skin lesions and joint pain

**Tests** in ulcerative colitis:

- Blood tests are done to check for anemia, which could indicate bleeding in the colon or rectum. The CRP may be elevated showing signs of inflammation.
- A stool sample can also reveal white blood cells, whose presence indicates ulcerative colitis or inflammatory disease. In addition, a stool sample allows the doctor to detect bleeding or infection in the colon or rectum caused by bacteria, a virus, or parasites.
- A colonoscopy or sigmoidoscopy are the accurate methods for making a diagnosis of ulcerative colitis and ruling-out other possible conditions, such as Crohn's disease, diverticulitis, or cancer.

**Treatment** Amoxicillin, tetracycline or metronidazole daily for 2 weeks should be given to eliminate *Fusobacterium varium*. Rest of medical management is described under the Crohns section.

**Autoimmune inflammatory gastritis (AIG), autoimmune atrophic gastritis, or autoimmune chronic gastritis:** The stomach acts as the storage area for meals and can hold up to 1.5 litres of food and fluid. Special cells (parietal cells) secrete hydrochloric acid that helps break down food in the stomach. Other cells release protein-digesting enzymes (pepsinogens) which become active in the acid environment and starts digesting protein. A substance called (intrinsic factor) which is necessary for the body to absorb vitamin B12 from the diet is also released here. Coordinated contractions of the stomach are important for grinding and mixing ingested food with the gastric secretions.

Autoimmune inflammatory gastritis (AIG) is a disease involving the stomach leading to shrinkage of the stomach (gastric atrophy), lowering of acidity (hypochlorhydria), and eventually to vitamin-b12 deficiency which causes a condition called pernicious anemia. *Helicobacter pylori* infection is the cause of chronic gastritis which if untreated progresses to atrophic gastritis. *H.pylori* gastritis is usually life long disease. Essentially atrophic gastritis is a result of molecular mimicry caused by the *h.pylori*. This leads to a hypo or achlorhydric stomach resulting also in B-12 deficiency. **In all the individuals presenting with B12 deficiency an evaluation needs to be done for autoimmune atrophic gastritis.** *Helicobacter pylori* infection is one of the most common bacterial infections in humans and it is associated with, chronic gastritis, duodenal or gastric ulcers, mucosal atrophy, gastric carcinoma and gastric lymphoma

#### **Symptoms of AIG:**

- A pain or burning ache indigestion in your upper abdomen that may become either worse or better when you eat
- Nausea and Vomiting, Loss of appetite, Weight loss
- A feeling of fullness in your upper abdomen long after eating
- Weakness, faintness, tired feeling, no energy, black or dark stools

#### **Diagnosis OF AIG:**

- **Upper gastrointestinal endoscopy.** An endoscope with a thin tube containing a tiny camera, through your mouth (or occasionally nose) and down into your stomach to look at the stomach lining and check for inflammation and may remove a tiny sample of tissue for tests. This procedure to remove a tissue sample is called a biopsy. AIG is characterized by lymphocytic infiltrates in the gastric mucosa biopsy
- **Blood test.** Red blood cell count to see whether you have anemia, which means that you do not have enough red blood cells. Anemia can be caused by bleeding from the stomach.
- **Stool test.** This test checks for the presence of blood in your stool, a sign of bleeding. Stool test may also be used to detect the presence of *H. pylori* in the digestive tract.
- **Serum anti-parietal cell autoantibodies** are detectable their level is higher during the early stages of inflammation, level is lower in atrophic stages and then risk of stomach cancer is relatively higher.
- **B12 Vitamin** B12 level may be low in the blood. Antibodies usually found in individuals with AIG are serum pepsinogen-I and *h pylori* antibodies.

**Treatment of autoimmune Gastritis:** *H. pylori* infection is etiologically associated with a number of important diseases including chronic active gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, gastric polyps, and gastric cancer. Treatment regimens include a two week bismuth-based “pepto bismol triple therapy for two weeks.

- Bismuth compound, metronidazole “Flagyl”, tetracycline or amoxicillin, or
- Ranitidine, bismuth citrate, metronidazole, clarithromycin.

These regimens achieve eradication rates of >> 80%. The antibiotics should be accompanied by a high fiber diet with fruits and vegetables multiple helpings during the day, eight glasses of water a day. It is recommended that individuals follow the Celiac disease guidelines look at the celiac section, by eating Fish, rice, milk, beef, chicken, vegetables, fruits and water. No wheat, millet, rye, oat, barley products should be taken. Milk or yogurt should be used at least 3 times a day. (100% milk)  
Anti-inflammatory treatment by using Fish oil is recommended. Vitamin B12 replacement by sublingual route should be advised.

**Gastric & Duodenal ulcer (Autoimmune):** The small intestine is divided into three functional regions: the duodenum, jejunum, and ileum. The stomach empties its contents into the duodenum, which is the first part of the small intestine. Here the contents are mixed with pancreatic enzymes (juices) and bile and most of the carbohydrates are absorbed in the duodenum. The cells lining the duodenum contains specialized groups of cells that produce chemicals which help digestion, provide immune defenses, and hormones that help to control coordination of digestive process of the intestine. These cells can be damaged by inflammation triggered by *Helicobacter pylori* (Hp), this causes Hp gastritis including duodenal ulcers, gastric ulcer, autoimmune gastritis, gastric carcinoma and gastric lymphoma.

The role of Hp in duodenal ulcerogenesis is not associated with acid hypersecretion. Ulcers in the duodenum are autoimmune as there is low yield of Hp in duodenal biopsy. This Hp induced autoimmune injury is an important mechanism in duodenal ulcerogenesis, it results in the release of inflammatory cells produced as a result of molecular mimicry into the gastric and intestinal lumen. It affects the duodenum with delayed gastric emptying which is a vicious cycle. The slower the emptying of food the higher is the exposure to inflammation leading to greater gastritis. Aspirin like drugs can make an ulcer worse make sure the affected person should stop taking these medications.

### **Symptoms:**

- **Pain** in the upper abdomen just below the sternum (breastbone) is the common symptom. It usually comes and goes (remitting relapsing). Abdominal pain can occur before meals, or when the person is hungry. It may be eased if you eat food, or take antacid medicines. The pain may wake the person from sleep.
- **Fullness** after a meal is felt by many people. Sometimes food makes the pain worse.
- **Bleeding** from the ulcer. This can range from a 'trickle' to a life-threatening bleed.

**Test:** Upper gastrointestinal endoscopy and H pylori antibodies are present..

**Treatment:** For ulcers caused by H. pylori, there are several treatment options. You can choose any single treatment option.

1. Metronidazole (500 mg twice a day) and clarithromycin (500 mg twice a day) and a proton pump inhibitor (such as omeprazole 20 mg twice a day) for 14 days.
2. Amoxicillin (1 gram twice a day) and clarithromycin (500 mg twice a day) and a proton pump inhibitor (such as omeprazole 20 mg twice a day) for 14 days.
3. Amoxicillin (1 gram twice a day) and metronidazole (500 mg twice a day) and a proton pump inhibitor (such as omeprazole 20 mg twice a day) for 14 days.
4. Bismuth subsalicylate (2 tablets 4 times a day) and tetracycline (500 mg 4 times a day) and either metronidazole (250 mg 4 times a day) or clarithromycin (500 mg 3 times a day) for 14 days.

After the person has completed one of the above regimens, they need to be continued on a proton pump inhibitor (Omeprazole), Cimetidine, Ranitidine, or sucralfate for an additional 4-6 weeks. This will help allow the ulcer to heal completely. This course of therapy should destroy the bacterium in more than 90% of people. There are increasing reports of H. pylori being resistant to metronidazole. Therefore, in areas where there is a lot of resistance to this antibiotic, the other treatment options are being used first. If the person is treated for H. pylori and the ulcer does not come back, no further evaluation or treatment is needed. If the ulcer does come back, then they need testing to see if the H. pylori have truly been destroyed. Please see the diet section on how to avoid H.pylori infections.

**Autoimmune acalculous cholecystitis ACC** (acalculous = no stone): The gallbladder is a small pear-shaped organ connected to the liver. The function of the gallbladder is to store bile which is made by the liver. Bile is a digestive liquid which emulsifies fats and neutralizes acids in partly digested food. The release occurs only with fatty foods.

Inflammation can occur in any organ and the gall bladder is not spared. Unlike stones causing obstruction and pain in inflammatory gall bladder disease, there is vasculitis. Inflamed blood vessels cut off the blood flow to this organ. On Ultrasound the gall bladder is enlarged, it may contain sludge. Usually the individuals have SLE or Sjogrens.

Microscopic examination of the gallbladder shows necrotizing angiitis of small arteries. Usually involves children, young women and rarely older men. The young women can have repeated attacks with multiple medical tests being negative, the diagnosis can be delayed for 8-10 months. **If this condition can be diagnosed early, treatment with steroids can avoid surgery.** It is estimated that cholecystitis occurs in 20 million people in the United States, and 500,000 people will undergo cholecystectomy annually.

**Symptoms of ACC:** Right upper abdominal pain. The pain is precipitated by fatty meals.

**Tests of ACC:** E.S.R. is elevated, CRP is elevated, white blood cells elevated in response to inflammation. Abdominal ultrasound and CT scan showed enlargement of the gallbladder and sludge without stones within the gallbladder. Antiphospholipid antibodies are positive.

**Treatment of ACC:** Early treatment with steroids can help avoid surgery. If Antiphospholipid antibodies are seen, subcutaneous or intravenous heparin and aspirin should be given, as severe multi organ failure can occur, due to blood clot formation and embolism. If steroids are not used and pain persists, then vasculitis will cause necrosis, within the gall bladder, which will require an emergency cholecystectomy.

**Autoimmune hepatitis:** The liver, located in the upper right side of the abdomen, acts as a filter to remove toxins (harmful substances) and waste products from the body, stores vitamins, minerals, and iron. It breaks down digested protein to amino-acids, eliminates chemicals from the body. All the blood coming from the stomach and intestines passes through the liver. The liver helps the body digest food and breaks down fats, by producing a substance called bile, which is stored in the gallbladder. Other functions, of the liver, include, processing hemoglobin and producing blood-clotting factors. A healthy liver, filters blood, at a rate of about 1.5 quarts per minute.

Autoimmune hepatitis is a disease in which the body's immune system is deceived to attack liver cells. This causes the liver to become inflamed (hepatitis). It occurs at any age and is more common among women than men between ages 12-40. About half of those have other autoimmune disorders, such as type-1 diabetes, kidney disease, thyroid disease, Sjogren's syndrome, autoimmune anemia, and ulcerative colitis.

Autoimmune hepatitis includes hepatitis-C (HCV), Epstein Bar Virus (EBV) and Celiac disease associated hepatitis.

**Symptoms:** Fatigue is the most common symptom of autoimmune hepatitis. Other symptoms include

- Jaundice, enlarged liver,
- Itching, skin rashes, (abnormal blood vessels) on the skin
- Abdominal discomfort & joint pain
- Nausea vomiting loss of appetite
- Dark urine pale or gray colored stools

**Diagnosis:** These individuals do not have hepatitis-A or B, they have hepatitis-C antibodies (anti-HCV positive), for at least six months and have no sign of any other chronic disease, such as liver failure, due to copper overload (Wilson disease), alpha-1-antitrypsin deficiency or liver failure due to iron overload called (haemochromatosis). Above diseases can be ruled out by obtaining copper levels in urine and iron levels in blood.

- **Blood tests.** A routine blood test for liver enzymes can help reveal a pattern typical of hepatitis, in autoimmune hepatitis; the immune system makes antinuclear antibodies (ANA), antibodies against smooth muscle cells (SMA), or liver and kidney microsomes (anti-LKM antibodies). The presence of these antibodies helps confirm the diagnosis of autoimmune hepatitis. Blood tests also help distinguish autoimmune hepatitis from viral hepatitis (such as hepatitis B or C) or a metabolic disease (such as Wilson's disease). Antibodies to check for celiac disease should be part of this evaluation. CRP and E.S.R. will be elevated.
- **Liver biopsy.** A tiny sample of the liver tissue, examined under a microscope, helps diagnose autoimmune hepatitis and tells how serious it is. Biopsy will show inflammation.

**Treatment:**

- Autoimmune hepatitis is treated with daily doses prednisone 20 to 40 mg per day and the dose can be lowered if the lab tests show improvement. The goal is to find the lowest possible dose that will control your disease. Treatment works best when autoimmune hepatitis is diagnosed early. In fact, recent studies show that sustained response to treatment not only stops the disease from getting worse, but may actually reverse some of the damage.
- Azathioprine (Imuran) is also used to treat autoimmune hepatitis. Like prednisone, azathioprine suppresses the immune system, but in a different way. It helps lower the dose of prednisone needed, thereby reducing its side effects. Azathioprine and prednisone can be used together once your disease is under control.
- Most people will need to take prednisone, with or without azathioprine, for years. Some people take it for life. Corticosteroids may slow down the disease, but everyone is different. In about one out of every three people, treatment can

eventually be stopped. The disease can go into remission, with a lessening of severity of symptoms. Some people with a remission will see the relapses or disease return, they just need longer immunosuppression. Supplement of garlic in hepatitis is recommended.

- In HCV positive disease interferon is used. If the antgliadin antibody is positive then please see the section for Celiac disease for dietary guidelines.

## Chapter 13 Autoimmune Hemolytic & Lymphoproliferative Diseases

**Autoimmune Lymphoproliferative Syndrome** (New disorder discovered by National Institutes of allergy and infectious diseases, if you have this disorder contact them for free treatment.) ALPS are a rare autoimmune disease that affects children and adults. ALPS stands for **A**utoimmune **L**ympho**P**roliferative Syndrome. The word *lymphoproliferative* describes the unusually large numbers of white blood cells (called lymphocytes) stored in the lymph nodes and spleens of people with ALPS. The word *syndrome* refers to the many common symptoms shared by ALPS individuals. Common autoimmune problems in ALPS include:

- Very low red blood cell counts (hemolytic anemia) that can make one weak.
- Very low platelet counts (thrombocytopenia or ITP) that cause bruises, nose bleeds, and pose a risk for hemorrhage (excessive bleeding). Little blue or reddish spots called petechiae may also show up on the skin.
- Very low white blood cell counts (neutropenia), risk for bacterial infection.
- Less often, other autoimmune problems can occur in any organ

The immune system of people with ALPS is efficient in fighting germs. The problem in ALPS begins after an infection is over. In ALPS, apoptosis (programmed cell death) does not work. Due to an excessive immune response, the white cells (lymphocytes) numbers are not reduced by the body, as it should after an infection is over. As a result, excess T and B cells gather in the lymph glands, liver and spleen. In ALPS, the B cells make a mistake. Instead of making antibodies against germs, the B cells make antibodies against platelets, red blood cells, or other cells. These antibodies become stuck to the platelets and red blood cells, which then get stuck in the spleen. The spleen has to work extra hard to filter out the sticky cells and the spleen gets big. There is a alteration in a gene to produce abnormal *Fas* protein. The *Fas* protein is one of several proteins that are important for apoptosis, the normal process through which cells die. *Fas* control the life span of certain cells, particularly the lymphocytes. Like people, cells have a normal life span in which they grow, do their job, and then die. The mutated *Fas* protein does not work well, and can't give the cells the message that it is time to die. There are many people who have no signs of ALPS, yet have a *Fas* mutation. Individuals with a *Fas* mutation have a 50/50 chance of passing the *Fas* mutation on to their children

**Symptoms:** Weakness, fatigue, tiredness, pale color, excessive bruising, bleeding from the gums, multiple infections. The abdomen is enlarged due to big spleen. Lymph nodes are enlarged all over the body.

**Tests:** CBC shows reduced red blood cells and increased lymphocytes, Platelets are reduced, Hemoglobin is reduced, Abdominal MRI will show an enlarged spleen, bone marrow biopsy and immunoglobulins test.

**Diagnosis:** Is based upon abnormal tests above and enlarged spleen, lymph nodes.

**Treatment:** Steroids are the first line of treatment for autoimmune episodes, like hemolytic anemia and *ITP*. One common steroid is prednisone. It is often given for a short time, but sometimes it is needed for longer periods. When prednisone is not enough to treat the episode, other drugs, such as Imuran and cyclosporin, may also be prescribed. Steroids have saved lives and have dramatically reduced the complications in some people with ALPS. However, like all treatments, steroids have some disadvantages.

- *Blood Transfusions* are useful to replace red blood cells when anemia is severe.
- *Vaccines* are important to help prevent infections. The fewer infections you have, the less often you will need to "call in the troops." In addition to all the childhood vaccinations, it is important to get a yearly flu shot and boosters as needed. People with allergies to eggs should discuss this with their doctor prior to receiving a flu shot.
- *IVIG and Rituxan* are future treatments for ALPS.

**Autoimmune Hemophilia:** Hemophilia has been called the Royal disease, it was seen in the European royal families, it is an inherited, bleeding and coagulation disorder. Children with hemophilia, lack the ability to stop bleeding, due to, low levels or absence of specific proteins, called "factors," in their blood. Clotting Factors, helps prevent excessive bleeding. There are many factors in the blood, which are involved in the function of forming clots to stop bleeding. A child with hemophilia is missing, or has a low supply of, one of the factors needed in order for the blood to clot. Two factors that affect blood clotting are factor VIII and factor IX. In about one-third of the children with hemophilia, there is no family history of the disorder. Yet some adults acquire this in later life. In late onset hemophilia the cause is mostly autoimmune and they have autoantibodies.

Neutralizing alloantibodies (inhibitors) to factor VIII or factor IX develop in approximately 25% of individuals with haemophilia-A and 3% of individuals with haemophilia-B treated with factor concentrate. **Individuals with high titre inhibitors do not respond to high doses of factor replacement and demonstrate resistance to treatment.**

**Symptoms:** Excessive bleeding due to poor clotting of blood.

**Test:** Neutralizing alloantibodies (inhibitors) to factor VIII or factor IX.

**Treatment** Alloantibodies against factors are rare but can cause life threatening bleeding, requiring costly, factor replacement and prolonged immunosuppression. These individual's have rapid resolution of the autoantibody, after treatment with **Rituximab** and low dose prednisone. Individuals receive, 375 mg m(-2) of intravenous rituximab weekly for 4 weeks, followed by monthly, (up to 5 months) until inhibitor disappearance and establishment of normal Factor VIII pharmacokinetics (recovery and half-life). Responses



continue off treatment from more than 7 to 12 months. If long term treatment is required then cyclophosphamide is used.

**Treatment of acquired Hemophilia.** After two plasmapheresis sessions, no subsequent bleeding episodes are seen. Inhibitor levels decrease to undetectable levels within a median of 3 days, factor substitution can be stopped within a median of 12 days. Long-term follow-up (7 months-7 years) showed an overall response rate of 90% for complete remission.

**The autoimmune hemolytic anemias (AIHA)** are rare disorders characterized by the premature destruction (hemolysis) of red blood cells, at a rate faster than they can be replaced. Acquired hemolytic anemias, are autoimmune diseases, which occur when the body's natural defenses against invading organisms destroy its own healthy tissues. Normally, the red blood cells (erythrocytes) have a life span of approximately 120 days before being removed by the spleen. Autoimmune hemolytic anemia occurs in different forms, including warm antibody hemolytic anemia and cold antibody hemolytic anemia. The appropriate therapy of autoimmune hemolytic anemia (AIHA) is dependent on the correct diagnosis and type of hemolytic disorder. Although, the majority of cases are warm AIHA, there are several distinct types of cold AIHA and a number of drug-induced etiologies of AIHA, which must be investigated, to determine if stopping a drug will induce a remission.

In warm antibody hemolytic anemia, the self-generated antibodies (autoantibodies) attach themselves and cause the destruction of the red blood cells, at temperatures above normal body temperature. In contrast, in the cases of cold antibody hemolytic anemia, the self-generated antibodies (autoantibodies) attach themselves and cause the destruction of the red blood cells at temperatures below normal body temperature.

There are other types of immune hemolytic anemias where the cause may result from an underlying disease or medication. Idiopathic autoimmune hemolytic anemia accounts for one-half of all immune hemolytic anemias. The onset of the disease may be quite rapid and very serious.

#### **Symptoms of AIHA:**

- Pale skin appearance
- yellowing of the skin, eyes, and mouth
- dark color to urine
- fever, weakness, dizziness, confusion
- intolerance to physical activity
- enlargement of the spleen and liver
- increased heart rate (tachycardia), heart murmur

**Test:** Autoimmune hemolytic anemia as the cause is confirmed when blood tests detect increased amounts of certain antibodies, attached to red blood cells (direct antiglobulin or Coombs test) Enzyme essays for antibodies against hepatitis-C, parvovirus B19 and Epstein-Barr virus.

#### **Treatment of AIHA:**

- In warm AIHA, corticosteroids intravenous pulses are standard, followed by consideration of splenectomy in difficult cases. If steroids and splenectomy are insufficient, other forms of immunosuppressive azathioprine is started. In cold AIHA, keeping the individual warm is often sufficient, but therapy directed at an underlying lymphoproliferative disorder may be helpful.
- Inadequate responses to therapy indicated by Hemolysis, and worsening anemia require transfusion therapy. When transfusion is urgently required and compatible blood cannot be located, incompatible blood may be provided as a life-saving measure.
- In the cold antibody type also known as paroxysmal cold hemoglobinuria, a disorder in which exposure to cold temperatures triggers massive hemolysis, is characterized by a unique biphasic cold autoantibody called the Donath-Landsteiner antibody. The treatment begins by keeping the individual warm, then plasmapheresis, prednisone, immunosuppressive drugs can be used.

**Iron-deficiency anemia:** Iron deficiency is the most frequently occurring anemia throughout the world. Blood loss is a major cause of iron-deficiency anemia. Gastrointestinal bleeding is the most common cause of iron deficiency in adult men and is second only to menstrual blood loss as a cause in women. Iron-deficiency anemia is not an autoimmune disease itself but a manifestation of an underlying autoimmune disease. Iron deficiency is a known complication of achlorhydria (reduced production of gastric acid) and may precede the development of pernicious anemia. (Vitamin B-12 deficiency anemia)

**.Symptoms and signs:** Persons suffering from iron deficiency anemia have pale skin color and experience shortness of breath, dizziness and frontal headache. Person cannot sleep well at night, due to continuous movements of legs (Restless leg syndrome).

- Tests: For iron status is the serum ferritin. C-reactive protein (CRP) should always accompany the analysis of serum ferritin. Routine blood tests to measure the size of the blood cells called CBC are done. Which show small size of red blood cells.
- Antigliadin –antibodies to check for celiac disease are obtained. H-pylori antibodies are checked and A.N.A antibodies for colitis are checked.

**Treatment:** Treatment needs to target replacing the iron stores is usually done with oral iron therapy. The main indications for parenteral iron therapy are intolerance to oral iron, intestinal malabsorption and poor compliance to an oral regimen. (The best treatment plan looks into what caused the poor absorption of iron, celiac disease, colitis or gastritis induced by H-pylori. Please look for proper treatment plan for each disease under the section of Gastritis.)

**ITP an autoimmune disease (Immune thrombocytopenia):**

Immune thrombocytopenic purpura (ITP) is an autoimmune bleeding disease. Immune refers to the immune system's involvement in this disorder. Antibodies, part of the body's immunologic defense against infection, attach to blood platelets, cells that help stop bleeding, and cause their destruction. Thrombocytopenia refers to decrease in blood platelets. Purpura refers to the purplish-looking areas of the skin and mucous membranes (such as the lining of the mouth) where bleeding has occurred as a result of decreased platelets.

Idiopathic thrombocytopenic purpura is among the diseases showing a stronger link with H. pylori infection. Review of the literature data shows that Helicobacter pylori eradication in individuals with idiopathic thrombocytopenic purpura is effective in increasing platelet count in approximately half of the cases. Acute (temporary) thrombocytopenic purpura is most commonly seen in young children. Symptoms often follow a viral infection. About 90 percent of children recover within a year and the problem doesn't return.

Thrombocytopenic purpura is considered chronic when it has lasted more than 6 months.

**Symptoms:** The main symptom is bleeding, which can include bruising "ecchymosis" and tiny red dots on the skin or mucous membranes "petechiae". In some instances bleeding from the nose, gums, digestive or urinary tracts may also occur. Rarely, bleeding within the brain occurs.

**Tests:** Blood tests to check for number of platelets, and to look for H. Pylori antibodies. A bone marrow test can be done to verify that there are adequate platelet-forming cells (megakaryocyte). This will help rule out cancer.

**Treatment:**

- Most individuals are given a short course of prednisone which usually gives a good response. Long term treatment with prednisone should not be given as it can cause cataracts or other neuromuscular complications.
- H. Pylori treatment should be given as half of the individuals will not require any future drug treatments after the eradication. Please look under autoimmune duodenal ulcer. IVIg treatments should be given to resistant cases. If H. pylori eradication is not done, IVIg treatment may not help. Many other drugs are used in the treatment please look under CIDP treatment section. Some people will do a splenectomy if everything else has failed.

**Lymphoma in autoimmune diseases:** Lymphomas result from increased lymphocytes (an immune cell). Abnormal production of proteins prevents the immune cells from dying when they should, also causing rapid cell division that produces more of its type. These malignant cells accumulate to form tumors that enlarge the lymph nodes and spread throughout the lymphatic system, including spleen or bone marrow. Lymphoma can also appear outside the lymphatic system.

Autoimmune diseases and lymphoma type malignancies are closely related. Lymphomas

may occur more frequently in the course of autoimmune diseases. An increased incidence of malignant lymphoma transformation has been described in individuals with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), and autoimmune thyroid disease. These individuals may generate autoantibodies against various autoantigens. Anti-ssDNA antibodies were detected in the sera of 25% of individuals with lymphomas.

Some common infective organism like, "H. pylori, C. jejuni, B. burgdorferi, C. psittaci, and hepatitis-C virus (HCV), which have been associated with gastric lymphoma, immunoproliferative small intestinal disease, cutaneous lymphoma, ocular lymphoma, and spleen lymphoma,. There appears to be a molecular mimicry type reaction resulting in the development of autoimmune lymphoma from these organisms.

Many organs can be targeted by an immune process due to the lymphoproliferative disease: they include skin diseases (paraneoplastic pemphigus, vasculitis, and urticaria), peripheral and central nervous system involvement (polyneuropathy, multifocal motor neuropathy), hematological manifestations (immune anemia, acquired bleeding disorders), rheumatologic diseases (arthritis, systemic vasculitis, and myositis) and renal lesion (cryoglobulinemia, glomerulopathies). A higher prevalence of autoantibodies, such as antinuclear antibodies, Antiphospholipid antibodies are seen in autoimmune lymphomas.

### **Symptoms:**

- Bone pain, arthritis
- Spinal cord involvement
- Anemia is seen with low levels of red blood cells, Low platelet levels, bone marrow
- hypogammaglobulinemia caused by a decrease in immunoglobulin production
- Enlarged lymph nodes are rubbery and discrete and later become matted.
- Waldeyer's ring (lymph-nodes around the tonsils) Lymph nodes in chest (Mediastinal) and abdomen (retroperitoneal) lymphadenopathy may cause pressure symptoms on various organs. (A) Congestion and edema of the face and neck can result from pressure on the superior vena cava (superior vena cava or superior mediastinal syndrome), and (B) ureteral compression from pelvic lymph nodes may interfere with urinary flow and cause secondary renal failure.
- The acute illness of adult T-cell leukemia-lymphoma is characterized by a fulminating clinical course with skin infiltrates, lymphadenopathy, hepatosplenomegaly, and leukemia. The leukemic cells are malignant. Hypercalcemia often develops in these cases.

**Tests: Antibodies for H. pylori, C. jejuni, B. burgdorferi, C. psittaci, and hepatitis C virus (HCV) should be tested. Biopsy of bone marrow and lymph nodes with MRI of the abdomen can be done.**

### **Treatment of Lymphoma:**

- Ocular adnexal lymphoma can be treated by doxycycline 300mg daily for 3 weeks.
- A subset of H. pylori-positive gastric MALT lymphomas, including infiltrative tumors, may respond to antibiotics. The likelihood of early complete remission seems to be greatest for superficial and distal tumor, amoxicillin 750 mg three times daily, and clarithromycin, 500 mg three times daily; combined with a proton pump inhibitor (lansoprazole or omeprazole) and bismuth subsalicylate. Eighty percent of gastric lymphoma are in continuous complete histologic remission.
- The monoclonal antibody anti-CD20 (rituximab), able to suppress the tumor cells and change the B-cell repertoire is the most promising treatment to cure immune disorders related to NHL. So far, rituximab has been successfully used in mixed cryoglobulinemia and cold agglutinins secondary to NHL.
- Nonresponders can be considered for surgery and/or chem/radiation therapy.

**Cryoglobulinemia:** The basic proteins-antibody that help fight against infecting organisms and allergies are called immunoglobulins. Normally, these immunoglobulins help the body fight infection. But when someone has cryoglobulinemia, these immunoglobulins clump together at low temperatures and cause organ damage and illness. Only three immunoglobulins (IgA, IgM and IgG) are involved in causing cryoglobulins. The cause of cryoglobulinemia is autoimmune, and there is an association with hepatitis C virus. Cryoglobulinemia may be associated with liver disease, infections, rheumatic disease, multiple myeloma or lymphoma. Cryoglobulins are abnormal forms of protein molecules that precipitate at cold temperatures and redissolve at normal body temperature. When a person with cryoglobulinemia is exposed to cold, they may experience impaired circulation in the small blood vessels due to clumping of these proteins. This may lead to color changes in the skin, hives, ulcers and bleeding into the skin (purpura). Cryoglobulinemia can affect anyone, but the majority of people with cryoglobulinemia are in their 40s or 50s. Twice as many women as men have this disorder. Cryoglobulinemia is not inherited. Cryoglobulins disease is subdivided into monoclonal if only one type of antibody is involved example IgM or polyclonal if multiple immunoglobulins are involved (IgG, IgM, IgA). However the treatment is the same regardless of which chains are involved. These disorders in a way are similar to Waldstrom's macroglobulinemia, monoclonal gammopathy of undetermined significance (MGUS) or its malignant form, multiple myeloma. All of which show abnormalities in immunoglobulins.

Cold agglutinins or cold autoantibodies are present in everyone at low titers. These natural cold autoantibodies occur at low titers of 1:60, normally and have no activity at higher temperatures. Pathologic cold agglutinins occur at higher titers and react at 29-30°C and sometimes at 37°C.

**Symptoms of Cryoglobulinemia:** Cold induced bleeding in the urine, or cold induced cough with bleeding, cold-induced skin rashes (urticaria), and arterial thrombosis with gangrene. In type-I when only a single monoclonal immunoglobulin is involved, bluish discoloration (cyanosis), retinal hemorrhage, cold hand (Raynaud's phenomenon), and arterial thrombosis are seen. Higher level of type-I cryoglobulins is associated with symptoms of hyperviscosity (poor circulation). .

The Type-II and Type-III cryoglobulins are mixed (IgG, IgM, and IgA), they may be associated with arthritis, vasculitis, renal failure (glomerulonephritis), strokes or seizures. In individuals with **mixed essential cryoglobulinemia (MEC)**, a syndrome may occur that is associated with arthritis, palpable purpura, weakness, palpable lymph-nodes and hepatosplenomegaly. Glomerulonephritis (renal failure) is common in MEC. The MEC syndrome is often sequelae of infection with Hepatitis-B or Hepatitis-C virus, and may respond to interferon therapy.

**Test :** Person may have anemia, low platelets, low white cell counts, complement blood levels show, Low C4 levels. Serum antibodies usually present are:

- § Hepatitis C virus (90%), Hepatitis B: Some individuals.
- § Anti-Nuclear antibodies, Anticardiolipin antibody.
- § Mycoplasma pneumonia antibodies.
- § Cold agglutinin titer is elevated 1:2,048.
- § Clonal B-cell infiltrates: Seen in Bone marrow or Liver biopsy.

**Treatment:**

- Warm blood transfusion is given, the individual is kept warm and immunosuppressive treatment with high dose steroids is effective. If the person has Mycoplasma infection, then Minocin is used for two weeks.
- For individuals with Hepatitis-C infection 6 or 8 million units (MU) of interferon alpha-2b every day for 2 weeks and then three times a week for 22 weeks with a daily dose of either 600 or 800 mg of ribavirin is helpful.
- Plasmapheresis and Rituximab are also useful in individuals who do not respond to primary treatments.

**Acute intermittent porphyria (AIP)** Porphyria has been suggested as an explanation for the origin of vampire and werewolf legends, based upon a number of similarities between this condition and the folklore. Similarity was based on people with porphyria having sun sensitivity. Porphyria cutanea tarda presents clinically as a pathological sensitivity of skin exposed to light causing scarring, skin and neurological symptoms. Porphyria is described here as it can be mistaken as an autoimmune disorder. It causes epilepsy, neuropathy, reversible encephalopathy, abdominal pain crises, liver failure, skin lesions and neuropsychiatric disturbances. In rare instances, however, AIP individuals have presented with acute cortical blindness. Extreme photosensitivity is seen in porphyria. Medical history has suggested that the insanity exhibited by King George III was the result of porphyria. British royal family (besides hemophilia), also carries a gene for porphyria. Porphyria is a complex disorder and eight sub-types have been described. Low plasma melatonin levels in porphyric women suggest that a defect of the pineal hormone may be responsible for the recurrent aspect of porphyric attacks.

**Symptoms: Cutaneous porphyrias** Sunlight triggered blisters, itching, and swelling of their skin.

**Symptoms acute porphyrias:**

- Pain in the chest, abdomen, limbs, or back;
- Numbness, tingling, paralysis, or cramping;
- Vomiting; constipation; and personality changes or mental disorders.
- Ultraviolet light transforms accumulated porphyrins in the skin into toxins that cause skin fragility. The dorsal surfaces of the hands are the principal sites of bullae formation because of exposure to sun and trauma. Shortly after bullae form, they rupture and become painful erosions that heal as atrophic scars and milia. Hypertrichosis (particularly involving the face and forehead), hyperpigmentation, hypopigmentation, and excessive wrinkling also may occur

**Testing:** Porphyria can be easily diagnosed by examining urine which turns dark on exposure to sunlight. Analysis of porphyrinogens in blood, urine and stool show significantly elevated values.

**Treatment:**

- Intravenous therapy with ham-arginate was and antiepileptic therapy with gabapentine works in AIP.
- Gabapentine is the only antiepileptic drug not metabolized by the liver and thus is safe in porphyria.
- A high carbohydrate diet is recommended in porphyria.
- Chloroquine (Aralen) Anti-inflammatory activity by and may have photoprotective effect. Use in porphyria requires small doses once a week. Larger doses may cause severe hepatic necrosis and death. Binds porphyrins and enhances excretion
- **Do Not Take These in Porphyria:** Barbiturates, Carbamazepine, Chloroquine, Ergotamines, Erythromycin, Estrogens, Ethanol, Ethosuximide, Fentanyl, Furosemide, Griseofulvin, Halothane, Hydralazine, Iron-compounds, Methyldopa, Nortriptyline, Phenytoin, Primidone, Pyrazinamide, Rifampin, Sulfonamides, Sulfonylureas, Theophylline, Tolbutamide, Valproic acid.

**Chapter 14 Ear Autoimmune disorders: Autoimmune inner ear disease, sudden hearing loss, vertigo or tinnitus & (Menieres)** Autoimmune inner ear disease or "AIED" consists of a syndrome of progressive hearing loss, noises in the ear or dizziness which is caused by antibodies, produced by our immune system, attacking the inner ear cells. The symptoms may remit and relapse and hearing loss can fluctuate between ears.

The ear is among the immune privileged areas, the body may not know about the inner ear antigens, and following injury they are released, then the body may mount an attack on these foreign antigens. Molecular mimicry triggered by a virus or bacteria also causes the immune system to generate antibodies causing accidental inner ear damage because the ear shares common antigens with a virus or bacteria.

Reduced hearing accompanied by ringing, hissing, roaring (tinnitus) which remits and relapses over months is commonly seen. Variants are bilateral attacks of hearing loss and tinnitus which resemble Menieres disease, and attacks of dizziness accompanied by abnormal blood tests for self-antibodies. Sudden onset of hearing loss is very common. Some individuals with AIED may have balance symptoms.

Autoimmune sensorineural hearing loss (ASHL) originally was defined by the presence of progressive hearing loss (with or without vertigo) and a positive response to (prednisone) therapy. The hearing loss can be of sudden onset in one or both ears. Usually the remitting relapsing pattern is seen. Hearing loss can be rapidly progressive sensorineural type.

AIED is usually seen in people with following disorders, Systemic Lupus Erythematosus (SLE), Sjogren's syndrome (dry eye syndrome), ulcerative colitis, Wegener's granulomatosis (runny nose, cough and kidney involvement), Bechet's, rheumatoid arthritis, and scleroderma (tight skin over hands and face) can cause or be associated with AIED.

**Symptoms** of AIED are sudden hearing loss in one ear; sometimes it may involve both ears. The hearing loss can progress over weeks or months, symptoms can be waxing & waning. Individuals may feel fullness in the ear and experience spinning attacks. Individuals also complain about something blocking the ear. Hearing may comeback.

**Test:** Antibodies to anti-68-kd antibodies, RPR to test for syphilis, antithyroid antibodies, antigliadin antibodies to test for celiac disease, Borrelia antibodies (IgG & IgM) for Lyme disease, E.S.R., CRP and ANA are done. CRP and E.S.R. are usually elevated. Ear testing will show sensorineural hearing loss.

**Diagnosis** of AIED is difficult and is often mistaken for otitis media, or sensorineural hearing loss. People with Menieres disease have AIED as the underlying cause. If the individual has other autoimmune disease or the CRP and E.S.R. are elevated the diagnosis can be based on them.

**Treatment:**

- Prednisone 20-40 mg daily for one day then 10 mg a day, and then taper over two months. E.S.R. should be checked and treatment should not be stopped if the E.S.R. remains elevated. Pulse treatment with high dose is more effective.
- Enoxaparin (Heparin) administered subcutaneously at a dose of 2,000 IU twice daily for 10 days will resolve AIED.
- Those individuals who do not respond to oral steroids can try intratympanic, the simplest procedure (and the least expensive) reported so far is that of Sennaroglu et al. They had simply had the individual administer dexamethasone themselves through a ventilation tube. A tube is placed in the posterior-inferior quadrant of the



TM. Individuals are instructed to lie on their side and place 5 drops into the affected ear once every other day. A low concentration of Decadron is used - 1 mg/ml.

- Immunosuppressive drugs including methotrexate, cyclophosphamide, azathioprine, mycophenolic mofetil, and intravenous immunoglobulin (IVIg) can be used if there is no response from the steroid treatment.
- Nystatin is a antifungal, has been found useful in a small study dosage is 500,000 units four times daily. As a powder, this is 1/8 teaspoon in an ounce or two of water; as a tablet, this is one tablet each dose; and as the suspension, this is one teaspoon per dose. It comes in many forms, including oral suspension (mixed in 50% sucrose to deaden its bitterness), oral tablets, powder, creams or ointments, and vaginal tablets. Those individuals on steroids can be weaned off.
- In the hyperbaric chamber, all individuals breathed 100% oxygen at 2.8 bars, for 60 minutes twice a day, either until recovered or for a maximum of 30 sessions. This treatment is still a investigational study as no dramatic improvements have been seen, some individuals complain about increased hearing loss related to high pressure on their ear drums from this treatment.

**Vogt-Koyanagi-Harada syndrome:** Vogt-Koyanagi-Harada (VKH) syndrome is a disease affecting several organs, eyes, ears, skin, hair and the nervous system. The etiology remains cell-mediated autoimmune disorder in individuals genetically susceptible to antigenic components of melanocytes. VKH usually occurs in adult life, in which severe bilateral inflammation of the iris (iridocyclitis), ciliary body and choroid of the eye is associated with relapsing meningitis, deafness, alopecia, depigmentation of the skin and eye, symmetrical loss of pigment (vitiligo) and whitening of the ends of the hairs (poliosis). There is a tendency towards recovery of sight, but it is not always complete. The syndrome usually occurs in young adults in Japan and Italy. Mental and growth retardation may occur in some rare familial cases. There is a association of hepatitis-C individuals, especially people with darkly pigmented skin who are being treated with interferon and ribavirin tend to develop VKH.

**Symptoms:** Inflammation and redness of eyes, retinal detachments, cotton-wool spots in fundus, headaches, ringing in the ears, and ordinary sound will appear uncomfortable like ringing of the telephone, someone speaking. Hair will start to fall out and start to turn white over the eyelashes, eyelids and patches of hair in the front.

- Bilateral chronic iridocyclitis (redness inflammation of the eye).
- Retinal-detachments, inflammation of the optic disc and iritis.
- Tinnitus (buzzing in ear), neck stiffness, memory problems.
- Alopecia, poliosis (patch of white hair), vitiligo (white patches).

**Treatment:** We think the treatment of the VKH syndrome should be early and aggressive.

- High doses of systemic corticosteroids and intravenous immunoglobulin, cycles.
- Individuals on interferon and ribavirin therapy need to be closely monitored for ophthalmologic complications, by periodic check-up of the optic fundi, for a

prolonged period, during interferon treatment as VKH can develop rapidly in these individuals. Please also see the CIDP treatment protocol for details.

## **Chapter 15 Endocrine Autoimmune disorders.**

**Sheehan's syndrome; or Empty Sella Syndrome; and relapsing remitting Lymphocytic Hypophysitis:** The pituitary gland lies within a bony cave called (sella turcica) at the base of the brain. Its small size at less 8 mm it controls all the hormones in the body. The pituitary gland has a central role in body growth, metabolism, and reproduction functions. It is connected to the brain by a thin (pituitary stalk) which is a direct extension of the hypothalamus (part of the brain which controls sex, weight, sleep, anger, blood pressure and temperature).

During pregnancy the pituitary gland enlarges and in rare case may develop inflammation. This inflammation during pregnancy has been called Sheehan's syndrome. If the swelling is severe it may cause blindness by compressing the visual tracts which are coming from the eye and heading toward the brain. Sheehan's syndrome usually presents as a visual disorder women are not able to lactate and developed reduced menstrual bleeding and later no menstrual periods (amenorrhea). This is a postpartum disorder due to inflammation within the pituitary gland. If the individual did not seek medical attention, then over the years they develop generalized edema, progressive s fatigue and weight gain. MRI scan done at this late stage of the autoimmune disease shows the usual atrophy of the pituitary gland, the radiological name for this is **empty sella syndrome**. Pituitary cell antibodies are usually positive in early stages. Recently individuals have been reported to have relapsing remitting symptoms of amenorrhea, visual changes, presenting with features of a mass lesion and loss of pituitary function. In these cases C.S.F. studies have shown increases white cells, biopsy shows lymphocytic hypophysitis and the swelling responds to steroids. In the long run if steroids are tapered the syndrome reoccurs, without treatment individuals eventually develop the empty sella syndrome (E.S.S.). Once ESS has developed the individual will need chronic thyroid replacement.

Here is a case study by Beressi N: A 25-year-old woman had headaches for a year after giving birth, associated with loss of menstrual periods and increased production of milk. M.R.I of the head revealed a enlarged pituitary gland; blood tests showed slightly elevated prolactin. Prolactinoma was diagnosed and bromocriptine was started at a dose of 5 mg daily, followed by restoration of the menstrual cycle. Two years later she developed adrenal insufficiency. M.R.I showed a pituitary mass was unchanged, but hormonal investigation showed complete hypopituitarism and no hyperprolactinemia. Nuclear antibodies were negative as well as other autoantibodies. Inflammatory-Lymphocytic hypophysitis was suspected; in the absence of visual complication, prednisone was started at a daily dose of 60 for 3 months. A gradual recovery of all pituitary hormones was observed and magnetic resonance imaging showed a reduction in the pituitary mass. Prednisone was progressively decreased within next six months. Six months after the end of steroid treatment, the individual relapsed with swelling of the pituitary. She underwent

steroid treatment, and a biopsy was performed and confirmed the diagnosis of autoimmune hypophysitis.

**Symptoms:** Rare first manifestations can be mental symptoms; depression, unable to concentrate, agitation, seizures, visual hallucination and sometimes have false beliefs. Common symptoms are visual loss, double vision, headaches; reduced or increased production of milk reduced or increased menstrual cycle. Increased thirst associated with fatigue and weakness. Rarely, a swelling develops in the neck due to thyroid inflammation.

**Blood tests:** Low sodium (hyponatremia) can be seen due to central diabetes insipidus. Normal or low levels of TSH, **ACTH**, FSH, and LH with low levels of T4, cortisol, and estradiol suggest Sheehan's syndrome. Low levels of IGF-I suggest growth hormone deficiency. MRI imaging is considered the optimal imaging technique for this area. It will show inflammation and mass, this is not a cancer. Prolactin levels are elevated. Spinal tap will show lymphocytes. If pituitary biopsy is done will show lymphocytic hypophysitis. Positive antibodies are ANA, antithyroid antibodies and pituitary cell antibodies, (antibodies can be absent in 30% of the cases). E.S.R. and CRP are usually elevated.

**Treatment:** steroid treatment should be started (125 mg methylprednisolone intravenously on days 1, 2, and 3, followed by 40 mg/d orally). As this is a chronic condition with relapses azathioprine should be started as an alternative long term treatment at a dose of 1 mg /kg. Individuals need a close follow up for monitoring E.S.R., clinical symptoms and dose of immunosuppressants should be adjusted based upon clinical tests. Steroids dosage can be tapered over two to three months. We re commend a long term 1-2 year treatment with Imuran. A daily aspirin should be given to all individuals. Surgery can be avoided in nearly all individuals.

**Hashimoto's Thyroiditis (also called autoimmune or chronic lymphocytic thyroiditis)** Hashimoto's disease is a problem with your thyroid gland located in your neck. The thyroid gland makes hormones called throxine that control how your body uses energy. When you have Hashimoto's disease, your immune system begins to attack your thyroid gland, causing it to become swollen and irritated. When this happens, your thyroid can't make hormones as it should. Although Hashimoto's disease can affect people of all ages, it's most common in women who are between 30 and 50 years of age. If someone in your family has had thyroid disease, you may have an increased risk for Hashimoto's disease. No one is sure why people get this disease. Hashimoto's is associated with Yersinia infection.

### **Symptoms of Hashimoto's Thyroiditis**

- Swelling of thyroid gland with fullness or tightness in the throat.
- Trouble swallowing food or liquids.
- Swelling or bump (called a goiter) in the front of your neck.
- Feeling of tiredness, forgetfulness,
- Depression, coarse dry skin, slow heartbeat,

- Weight gain, constipation and intolerance to cold.
- Many people with this disease have no symptoms at all.

**Test:** Blood test testing for T3, T4, TSH and antithyroid antibodies.

**Treatment:**

- Most doctors recommend synthetic thyroxine (levothyroxine), Synthetic thyroid medications contain thyroxine only, and the triiodothyronine your body needs is derived from the thyroxine.
- Natural extracts containing thyroid hormone derived from the thyroid glands of pigs are available. These products contain both thyroxine and triiodothyronine. Extracts are available by prescription only
- Glandular concentrates sold in natural foods stores are dried concentrates of glands derived from animals. These products aren't regulated by the Food and Drug Administration, and their potency isn't guaranteed.

**Graves Disease:** Graves disease in which the immune system over stimulates the thyroid gland, causing hyperthyroidism. Over-activity of the thyroid is sometimes named "diffuse toxic goiter." The thyroid gland helps set the rate of metabolism (the rate at which the body uses energy), and when it is over-stimulated, it produces more thyroid hormones than the body needs. High levels of thyroid hormones can cause difficult side effects. This is a rare disease that tends to affect women over the age of 20. The incidence is about 5 in 10,000 people.

**What are the symptoms of Graves 'disease:**

- Insomnia, irritability, weight loss without dieting,
- Heat sensitivity, increased perspiration,
- Fine or brittle hair, muscular weakness,
- Eye changes, lighter menstrual flow,
- Rapid heart beat, and hand tremors.

Grave's Disease is the only kind of hyperthyroidism that is associated with inflammation of the eyes, swelling of the tissue around the eyes, and protrusion, or bulging, of the eyes. Some individuals will develop lumpy reddish thickening of the skin in front of the shins called pretibial myxedema. This skin condition is usually painless. The symptoms of this disease can occur gradually or very suddenly and are sometimes confused with other medical problems. Women can have Grave's Disease and have no obvious symptoms at all.

**Tests:** TSH level, T3, T4 and antithyroid antibodies.

**Treatment:**

- To lower the amount of thyroid hormones produced by the body, the medication used are methimazole (Tapazole) or propylthiouracil (PTU) pills. These drugs act to prevent the thyroid from manufacturing the thyroid hormone.

- **Surgery:** Part or all of the thyroid gland will be removed. In most cases, people who have surgery for Graves disease will develop an under-active thyroid (hypothyroidism), and will have to take thyroid replacement hormones for the rest of their lives.
- **Radioactive iodine:** The iodine damages thyroid cells to shrink the thyroid gland, to reduce hormone levels. Like surgery, this condition usually leads to hypothyroidism, requiring medication for the rest of the individual's life.

**Autoimmune Diabetes Insipidus:** Diabetes Insipidus (DI) is a disorder in which there is an abnormal increase in urine output coupled with higher fluid intake and thirst. Autoimmune DI is highly likely in young individuals with a clinical history of autoimmune diseases and radiological evidence of pituitary stalk thickening. Pituitary gland is the master gland which controls the body's hormones, thickening of the stalk is a indication of inflammation. Demonstration of autoantibodies against AVP-cells of the pituitary in the serum of individuals with so-called idiopathic diabetes insipidus indicates an autoimmune basis of the disease. This interpretation of the new antibody results is supported by a frequent association of idiopathic diabetes insipidus with recognized auto-immune diseases. The disease can be triggered by many infections including Malaria, T.B. and other autoimmune diseases.

**Symptoms** consist of urinary frequency, frequent awakening at night to urinate (nocturia) or involuntary urination during sleep or "bedwetting". Urine output is increased as it is not concentrated normally. Instead of being a yellow color, the urine is pale, colorless or watery in appearance and the concentration (osmolality or specific gravity) is low.

**Test:** Autoantibodies against vasopressin (AVP)-producing cells of the human pituitary gland as well as conventional antibodies have been seen with central diabetes. MRI scan of the head will show thickening of the pituitary stalk, (request the radiologist to focus on the pituitary stalk). Thiamine blood levels should be checked to look for a deficiency. Sed rate can be elevated.

**Treatment:**

- Use of short trial of prednisone should resolve all inflammation and resolve the higher fluid intake.
- Desmopressin DDAVP treatment initiated leads to a normalization.
- Thiamine 75mg/day replacement if deficiency is found.

Rarely D.I will be associated with anemia, thiamine and thiamine pyrophosphokinase (TPKase) enzyme deficiency, diabetes mellitus, sensorineural deafness and thiamine-responsive megaloblastic anemia. If treated with Thiamine therapy started at 75 mg/day. With Thiamine treatment Insulin requirement decrease eventually stops. The macrocytic

anemia improved with thiamine treatment. This syndrome is called DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, deafness).

**Diabetes mellitus:** Insulin dependent diabetes mellitus (IDDM or type-1) is an inflammatory autoimmune disease of the pancreas, resulting in a lack of insulin. Today, the autoimmunogenesis of type-1 diabetes mellitus is unquestioned. Evidence for this includes the detection of specific antibodies, an association with other autoimmune diseases. New evidence suggests that beta-cell regeneration is possible, but ongoing autoimmune damage prevents restoration of beta-cell mass. The actual trigger that leads to the loss of immunotolerance has not so far been identified. It is probable that a complex interaction of environmental and genetic factors underlies the manifestation of type-1 diabetes mellitus. The prevalence of celiac disease in diabetic children and adolescents in diabetes is elevated, being comparable with levels observed in studies in North America and Europe and lower than in Africa, suggesting that serological screening for celiac disease be performed for all children and adolescents with type-1 diabetes mellitus. Insulin is produced in the pancreas by beta cells. The main source of energy for all cells and especially for brain cells is glucose. Insulin is necessary for glucose to get into cells and be used for energy production. After eating, the level of glucose rises in the blood, which leads to insulin being released from the pancreas. In a person with damaged, beta cells causes an insufficiency of insulin.

Type 2 diabetes (non-insulin-dependent diabetes mellitus) Insulin concentrations are mostly increased but peripheral tissues are resistant to insulin (insulin resistance). Beta cells are not able to increase secretion of insulin to overcome this resistance. Type-2 diabetes usually develops after 40 years of age in overweight people, lately in obese adolescents.

Gestational diabetes mellitus: or type -II is characterized by insulin resistance, have positive pancreatic islet antibodies, especially to glutamic acid decarboxylase (GAD). They do not immediately require insulin for treatment, are often not overweight, and have little or no resistance to insulin.

The following evidence exists that diabetes type-1 is an autoimmune disease:

- Association with other autoimmune diseases – pernicious anemia, Addison's disease, autoimmune thyroid disease
- Lymphocytic infiltration around the islets of Langerhans in the pancreas.
- Immunosuppressive treatment is able to delay onset of disease.
- Autoantibody presence in serum:

- ICA (Islet cell antibodies) - against the antigen present in the cytoplasm of the endocrine cells in pancreatic islets.
- IAA (Insulin autoantibodies) is present.
- GAD – autoantibodies to glutamic acid decarboxylase is present.

**Symptoms:** Excessive urination, intense thirst, dehydration and mineral loss. Weight loss: Because of the insufficient level of insulin, glucose can not be used as a energy source.

**Diagnosis:** High glucose level. In the case of doubts in the beginning of the disease, the level of glucose is measured after 12 hours of fasting (Fasting Plasma Glucose Test). If this test is not conclusive, Oral Glucose Tolerance Test may be used to confirm the diagnosis. Islet-cell and anti-insulin autoantibodies are positive only in the beginning of IDDM. The test called hemoglobin A1C is elevated in diabetes.

**Incidence:** People under the age of 40. The disease often starts in childhood and affects more Caucasians than African-Americans. The male-to-female ratio is 1:1.

**Treatment:**

- Insulin is used as a substitute for the lost beta cells function. However, it does not treat IDDM. It has to be used life-long, several times per day in subcutaneous injections before meals. The proper dosage of insulin and appropriate menu plans have to be determined by a doctor. It is very important that individuals follow the recommended doses and menu plans and that they regularly monitor their level of glucose in blood (which should be kept at 80–140 mg/dl). Good management of IDDM also requires good individual (or parent) education about the roles of sport, diseases, and food in maintaining a stable glucose level. As regards food, the diabetic diet is not sugar-free but rather a balanced diet with a carefully controlled calories intake and regular timing. Regular follow up is absolutely essential to avoid long term complications.
- Findings suggest that **vitamin D3** may be an important pathogenic factor in type 1 diabetes, and that its supplementation should be considered not only at birth, but also at diagnosis of type 1 diabetes with the aim of protecting residual beta cells from further destruction these results are based on multiple studies.
- **Pancreatic islet cell transplantation** is an attractive treatment of type 1 diabetes (T1D). The success enhanced by the Edmonton protocol has fostered phenomenal progress in the field of clinical islet transplantation in the past 5 years, with 1-year rates of insulin independence after transplantation near 80%. Long-term function of the transplanted islets, however, even under the Edmonton protocol, seems difficult to accomplish, with only 10% of individuals maintaining insulin independence 5 years after transplantation

**Addison Disease:** Addison's is an uncommon autoimmune disease, characterized by reduced functioning of the outer layer of the adrenal gland. The adrenal glands are located on top of each kidney and produce steroids (glucocorticoid hormones). A person with Addison's disease will have a deficiency in the producing glucocorticoid hormones (GH). These hormones are named GH as they are involved in how the body utilizes and stores **carbohydrates**, protein, fat and blood sugar. The adrenal gland produces Cortisol, the production is controlled by the pituitary gland in the brain. The Pituitary produces a hormone called ACTH which stimulates the adrenals to make cortisol. (ACTH is **adrenocorticotrophic hormone**)

A deficiency in glucocorticoid hormones causes an increase in the release of sodium and a decreased release of potassium in the urine, sweat, saliva, stomach and intestines. These changes result in low blood pressure and increased water excretion that can in some cases lead to dehydration. The adrenal gland also plays a role in the immune response.

Majority of Addison's disease cases are caused by autoimmune process. The first case with Addison was caused by tuberculosis which remains as the commonest cause of Addison's. John Kennedy suffered from Addison's disease, his political career was made possible due to administration of cortisol.

#### **Symptoms in Addissons:**

- General weakness and becoming easily tired.
- Dark areas of skin. Seen in the arm-pits, the nipples, the creases of the hands, inside the mouth, recent scars, and elbows.
- Blood pressure is low and falls when on standing which can make you dizzy.
- Nausea, vomiting and weight loss.
- Abdominal pains which wax and wane.
- Diarrhea or constipation which wax and wane.
- Cramps and pains in muscles with craving for salty foods and drinks.
- Menstrual periods become irregular, or stop.
- **Sudden symptoms of**, severe vomiting, diarrhea, abdominal pain, dehydration, low blood pressure and unconsciousness are caused if the level of cortisol falls this is called an **Addisonian crisis**.

#### **Diagnosis of Addison's disease:**

- Cortisol levels in the blood.
- ACTH stimulation test to check if adrenals inability to produce cortisol.
- Insulin test to check diabetes.

#### **The treatment of Addison's disease:**

- The usual replacement dose of Hydrocortisone is 20 mg first thing in the morning and 10 mg at 6 pm.
- ACE (adrenal cortical extract). ACE is a blend of all 50 or so hormones made by the adrenal cortex and is the alternative medicine that can be used for addisons..



## **Chapter 16 Autoimmune Gynecological / Obstetrics diseases.**

**Autoimmune Endometriosis:** Endometriosis occurs when tissue lining the uterus (endometrium) is found outside the uterus. This displaced tissue develops lesions which respond to the menstrual cycle monthly. Endometrial tissue builds up, breaks down, and sheds in monthly cycles. Menstrual blood flows from the uterus and out of the body through the vagina, but the tissue shed from extrauterine endometrial lesions has no way of leaving the body. This results in internal bleeding, and inflammation resulting in pain, infertility, scar tissue formation, adhesions, and bowel problems. Women with endometriosis frequently suffer from autoimmune inflammatory diseases, hypothyroidism, and fibromyalgia (FM), chronic fatigue syndrome (CFS), allergies and asthma. These findings also suggest a strong association between endometriosis and autoimmune disorders and indicate the need to consider the co-existence of other conditions in women with endometriosis. Women with endometriosis also have higher than expected rates of autoimmune inflammatory diseases including systemic lupus erythematosus, Sjogren's syndrome, and rheumatoid arthritis, as well as multiple sclerosis. Typically a 10-year delay between the onset of pelvic pain and diagnosis of endometriosis is seen.

In women who have endometriosis, tissue similar to the lining of the uterus the endometrium grows in other parts of the abdominal cavity. The endometrial tissue may attach itself to the ovaries, the outside of the uterus, the intestines, or other abdominal organs. Endometriosis affects an estimated eight to ten percent of reproductive age women. It may cause infertility or pelvic pain, although some women with the disease may not experience symptoms. In addition, family members of women with endometriosis have the disease. Subacute focal endometritis has been associated with cervical *Ureaplasma urealyticum* colonization and *Chlamydia trachomatis* are considered a factor in pelvic adhesions or endometriosis.

**Symptoms:** Women experience pelvic pain usually for about 10 years before they are diagnosed with endometriosis. In women the pain starts shortly after their first periods. The pain usually varies during the menstrual cycle. Menstrual irregularities, heavy menstrual bleeding and spotting before menstrual periods, may occur. Cramps and pain, caused by the misplaced tissue are seen during menstruation, often causing, and recurrent first-trimester miscarriages. Pain occurs during sexual intercourse. Some women have back pain.

**Tests:** Thyroid antibodies and thyroid blood tests (TSH, T3, T4). Anti-laminin-1 autoantibodies may be present confirming the diagnosis of endometriosis. ANA is positive. CA-125 is elevated in the blood. MRI and ultrasound will show lesions in the pelvis.

### **Treatment:**

- Zithromax (250-mg once a day for eight days is given to all individuals to clear up any infection associated endometriosis like (chlymadia). The vaginal pain in this

condition is successfully treated with immune-modifying drugs. Hydrocortisone acetate 10% foam helps control pain in the vagina. In non responders Hydroxychloroquine, an immune-modifying, antirheumatic drug, is added for relief along with hormone treatments. Methotrexate has been used to help control the symptoms of pain.

- Before in vitro fertilization (IVF) Tetracycline (5%) (5-10 mL) is instilled into the endometrioma cyst and the cyst contents are sequentially aspirated and flushed with sterile saline until the aspirated fluid was clear. Saline is injected into the cul-de-sac to dilute any tetracycline that may have leaked. The fluid is then removed. Ultrasound is performed 6 weeks later to assess the efficacy of treatment. Treatment can be repeated if the endometrioma cyst persists.

### **Recurrent Spontaneous Abortion: Recurrent Miscarriage Syndrome**

**(RMS):** Recurrent miscarriage syndrome and infertility are common problems in the United States. Recurrent miscarriage affects more than 500,000 women annually. If properly screened through a protocol, the cause will be found in almost all women. The most common defect in women with RMS is a homeostasis defect associated with Antiphospholipid syndrome. Other hereditary and acquired procoagulant defects are also commonly found, if looked for. It is important to evaluate women with RMS appropriately, because if a cause for the RMS is found, most women will achieve normal-term delivery. More than 98% will have a normal term delivery with preconception aspirin (ASA) and addition of postconception heparin to be continued to term. Individuals should be screened by an obstetrician or by reproductive specialists for hormonal and anatomic defects before initiating a procoagulant evaluation; if such prescreening is done, the yield of this therapy leads to an excellent outcome.

**Symptoms:** recurrent abortion or miscarriage.

**Test:** antiphospholipid antibody, Anti nuclear Antibody, Antigliadin antibody need to be tested to check for celiac disease.

**Treatment** of the common procoagulant defects consists of preconception low-dose ASA at 81 mg/day followed by immediate postconception low-dose fractionated porcine heparin at 5000 U every 12 hours was added immediately postconception; both agents were used to term delivery. (Please also read the section of antiphospholipid syndrome).

**Male -Infertility:** As many infections can be present in the urinary tract, uterus, vagina and hymen. These can trigger autoimmune inflammatory reactions causing pain, itching and infertility. Many other studies show that mycoplasma or ureaplasma most common cause of infertility is a uterine infection. Fifty percent of women are infected with Chlamydia, mycoplasma or ureaplasma, and fifty percent of those with tubule blockage. The more partners you have, the more likely you are to be infected, although you can be infected by one contact. An infection can prevent pregnancy by blocking the uterine tubes.

The infection can produce antibodies against sperm so that they can't swim toward the egg, antibodies can cause abortions, premature birth and low birth weight.

Some of the men have are infertile as they have **antisperm antibodies**. These people have no other symptoms other than a abnormal antibody.

**Symptoms:** Infected people may have burning on urination, discomfort when the bladder is full, or an urgency to void. Women may have only spotting between periods.

**Test:** A dipstick urine test may diagnose the infection. Men with a history of infertility should be tested for antisperm-antibodies

**Treatment:**

- Zithromax (250-mg once a day for eight days) or Biaxin (500-mg BID for 10 days), for Chlamydia and mycoplasma infections. We recommend that both the partners have to be treated or failure rates will be higher.
- Treatment for those men who have antisperm-antibody is to take prednisolone, 40 mg a day, for the first 10 days, then 15 mg on days 11 and 12 of the partner's cycle for 3-9 months.

**Eclampsia- Preclampsia:** Preeclampsia, called toxemia, is a problem that occurs in some women during pregnancy. It can happen during the second half of pregnancy with symptoms of high blood pressure, swelling of hands, feet and protein in the urine. Some of those suffering from preeclampsia can develop eclampsia which consists of additional symptoms of seizures. Eclampsia is commonly in individuals with autoimmune diseases thus we present some simple ways to diagnose the individuals who will develop eclampsia and provide treatment guidelines. Pre-eclampsia develops in the interaction between the placental disease and maternal responses. Pre-eclampsia probably is auto-immune, with the auto-antibodies directed against certain types of phospholipids or trophoblastic constituents. Eclampsia is defined as seizure activity or coma in an obstetrical individual with preeclampsia. Eclampsia commonly present in the third trimester of pregnancy or within the first 48 hours following delivery, rare cases can be seen prior to 20 weeks' gestation or as late as 20 days postpartum. Eclampsia can occur without prior development of preeclampsia. Preeclampsia is a disorder a resulting from systematic inflammatory maternal reaction. **CRP** is a positive marker of inflammation, higher levels of CRP are present in preeclampsia than in normal pregnancy. It has been reported that in autoimmune individuals platelets are presensitized or are relatively inflamed, which indicates a subgroup of women can benefit from low-dose aspirin in the prevention of thrombosis. We recommend monitoring the CRP levels late into the pregnancy which will indicate the individuals most likely to develop eclampsia.

**Symptoms & Findings** in pre-eclampsia: Pre-eclampsia causes renal, hepatic, myocardial, cerebral and adrenal ischaemia - that is ischaemia in all highly vascular organs. Placental

ischaemia, like ischaemia in all other organs, is a consequence of eclampsia. Seizures, headaches, coma, renal failure can happen during eclampsia.

**Tests:** CRP monitoring, serum homocysteine, B-12, B-6, Folic acid levels should be done. Antiphospholipid antibodies should be checked.

**For treatment:**

- Low dose heparin or aspirin to desensitize platelets and to use magnesium sulphate if any seizures develop. Aspirin lowers the risk of complication in the mother and baby by 15%.
- Magnesium sulfate is an anticonvulsant and helps prevent seizures and maintain uterine and fetal blood flow. Can be administered IV and IM (intramuscular). Intravenous route is preferred over IM route as administration is controlled easily. The goals of magnesium therapy are to terminate seizures. Individual should be evaluated to assure that deep tendon reflexes are present, respirations are at least 13 breaths per min, and urine output is at least 100 mL during the preceding 3 h. When using magnesium sulfate IV, close monitoring of individual and fetus is necessary. Magnesium therapy usually is continued for 12-24 hours following delivery and may be stopped when the hypertension resolves and the individual has shown adequate urine production. Renal impaired individuals should be monitored with magnesium levels, with aggressive adjustments made to achieve levels at 6-7 mg/dL.
- IVIg treatment has been shown to control all symptoms of eclampsia and is safe during pregnancy.
- For individuals with elevated homocysteine use sublingual or intramuscular B6, B-12 and Folic acid replacement. Those who have antiphospholipid antibodies need subcutaneous heparin. Coumadin started at the time of preeclampsia results in normal delivery.

**Chronic Pelvic pain & Pelvic inflammatory disease:** Chronic pelvic pain is a autoimmune disorder, this is also one of the most preventable conditions. Chronic pain starts with pelvic inflammatory disease. Pelvic inflammatory disease, the infection and inflammation of the female upper genital tract, is a common cause of infertility, chronic pain and ectopic pregnancy. Since pelvic inflammatory disease has a multimicrobial etiology including *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and anaerobic and mycoplasmal bacteria, treatment of pelvic inflammatory disease should consist of broad spectrum antibiotics. Pelvic inflammatory disease (PID) is an infection of the upper genital tract in women that can include endometritis, parametritis, salpingitis, oophoritis, tubo-ovarian abscess, and peritonitis. It affects up to 1.5 million women in the United States and costs an estimated \$1.06 billion each year. The etiologic agent often is never identified, but common causal agents are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

**Symptoms:** Symptoms of PID include lower abdominal pain, painful menstrual cycle, fever, back pain, and vomiting, as well as symptoms of lower genital tract infection such as

abnormal vaginal discharge or bleeding, itching, and odor. In some women, symptoms are mild or even absent.

- Elevated erythrocyte sedimentation rate or C-reactive protein.
- Laboratory confirmation of gonorrheal or chlamydial infection.
- Oral temperature of 101°F (38.3°C) or greater.
- White blood cells on vaginal secretion saline wet mount.

**Test:** PID and may be evaluated by urine and vaginal swab testing instead of speculum and bimanual examination. Cervical or vaginal mucopurulent (green or yellow) discharge

Transvaginal ultrasound, computed tomography, and magnetic resonance imaging (MRI). The classic findings of acute PID on transvaginal ultrasound are tubal wall thickness greater than 5 mm, fluid in the cul-de-sac.

#### **Diagnosis and management:**

- Cefotetan (Cefotan) 2 g IV every 12 hours or cefoxitin (Mefoxin) 2 g IV every six hours ; plus doxycycline (Vibramycin) 100 mg orally or IV every 12 hours
- Clindamycin (Cleocin) 900 mg IV every eight hours; plus gentamicin loading dose IV or IM (2 mg per kg) followed by a maintenance dose (1.5 mg per kg) every eight hours (single daily dosing may be substituted)
- Ofloxacin (Floxin) 400 mg IV every 12 hours or levofloxacin (Levaquin) 500 mg IV once daily; with or without metronidazole (Flagyl) 500 mg IV every eight hours
- Ampicillin/sulbactam (Unasyn) 3 g IV every six hours; plus doxycycline 100 mg orally for 14 days.
- Ceftriaxone (Rocephin) 250 mg IM in a single dose or cefoxitin 2 g IM in a single dose with concurrent probenecid (Benemid) 1 g orally in single dose or other parenteral third-generation cephalosporin; plus doxycycline 100 mg orally twice daily for 14 days with or without metronidazole 500 mg orally twice daily for 14 days.

## **Chapter 17 Respiratory autoimmune Disorders**

**Asthma:** Asthma starts like an allergic disease and with repeated exposure to allergens turns into an autoimmune disease, it affects the small airways (bronchioles) that carry air in and out of the lungs. The airways can become inflamed, swollen and constricted (or narrowed), with excess mucus being produced. Asthma can affect anyone, at any age, anywhere. An asthma 'attack' consists of a wheezing or whistling noise in the chest, coughing and difficulty breathing that occur when the airways become narrowed, inflamed and blocked by plugs of mucus. Recently, chronic **Chlamydia pneumoniae** infection has been suggested as a cause for adult-onset asthma. Higher levels of C-pneumonia are found

in children with recent asthma attacks. Allergic form of asthma can be triggered by any food including carrots, by metal dust in nickel cobalt and even dust mites. In a group of children with asthmatic mothers, those exposed to cats were more likely to wheeze as compared to those with no cat exposure. The risk of wheezing increased in each of the five years of the child's life. By the third year, the risk of wheezing doubled, and by the fifth year it more than tripled. Children of asthmatic mothers become more readily sensitized to cat allergens.

**Tests:** In infants with asthma, Umbilical **erythema (Red Umbilicus)** can be a sign of food intolerance specially an allergy to milk. Test for food and milk allergies should be done. In children with bilateral otitis the common cause of asthma is milk allergy. Tests for Mycoplasma pneumonia antibody need to be done in adults. Test for antigliadin antibodies and anti-H.Pylori antibodies

### **Treatment of asthma:**

- In infants with the red umbilicus, otitis media (ear infections) and those that show allergies to milk, all milk products should be removed. They can be given soy milk. This will resolve the asthma issue. In resistant cases individual will need to be placed on gluten free diet please see the celiac disease section. In adults a search should be done for Mycoplasma and then 4 weeks course with oral doxycycline (100 mg twice daily), azithromycin (1000 mg once weekly), or erythromycin (1000 mg daily) be given. If a mild benefits is seen in asthmatic individuals then minocycline 100 mg daily may be used for additional two weeks. Antimicrobial therapy appeared to "cure" or significantly improve asthma in approximately one half of treated adults.
- Intravenous Magnesium sulphate infusion 40 mg/kg doses (maximum 2 g) can cause bronchodilation in treatment of severe asthma, 2.5 mg nebulised salbutamol mixed with either 2.5 mL isotonic magnesium results in an enhanced bronchodilator response in treatment of severe asthma.
- The allergen causing asthma should be avoided. Steroids, inhalers and epinephrine are used for long term asthma management.
- People with asthma are sensitive to pollen concentration and carbon dioxide (CO<sub>2</sub>) concentration. CO<sub>2</sub> concentration is higher at night under trees and lower altitudes. Classrooms may have higher concentration of CO<sub>2</sub>.
- Nebulized MgSO<sub>4</sub>, particularly in addition to a beta2-agonist, in the treatment of an acute asthma exacerbation appears to produce benefits with respect to improved pulmonary function and may reduces the number of hospital admission.
- 2 g of IV or 40 mg/kg magnesium sulfate improves pulmonary function when used with standard therapy in individuals with very severe, acute asthma.(specially in children)
- Children with documented cat allergy or with asthmatic symptoms triggered by a cat should also avoid cats.

- In rare cases where asthma is still not controlled a course of IVIg can be used.

**Sarcoidosis:** Sarcoidosis is a multi-systemic disease in which the immune system starts to attack multiple organs. This over-reaction by the immune dysfunction is characterized by the formation of granulomas (inflammatory masses) in the affected organs. Granulomas are clumps formed by cells of the immune system lumping together. Granulomas can appear on the walls of the alveoli (small air sacs in the lungs) or on the walls of the bronchioles (breathing tubes in the lungs). Current estimates show that over 50 percent of people with sarcoidosis will get well within a year without treatment. The disease has remitting and relapsing periods just like any other autoimmune disease. It closely resembles tuberculosis, berylliosis (metal poisoning caused by inhalation of beryllium dusts), and many autoimmune diseases. The resemblance to TB causes some to think that sarcoidosis is triggered by a infectious organism, but it is yet to be proven, genetic factors and autoimmunity are considered as etiologic agent in Sarcoidosis. Following BCG vaccination cases of sarcoidosis have been reported and mycobacterium DNA and antibodies have been found in sarcoidosis. Although once thought to be a rare disease, with better diagnostic procedures and disease tracking, sarcoidosis is becoming more commonly recognized. With the high occurrence of lung involvement sarcoid is believed to be something that is inhaled. This may include a toxin, allergen or other environmental exposure. There is a genetic predisposition that makes some people more susceptible than others who get sarcoidosis. Excessive exposure to sunlight and high vitamin-D levels can cause the chronic inflammation in sarcoid.

**Symptoms of sarcoidosis:** Many individuals have no symptoms, and the diagnosis is made almost accidentally through routine testing or x-rays.

- Fatigue, weakness, fever, abdominal pain and weight loss.
- Dry cough (without sputum), shortness of breath, or mild chest pain.
- Scaly rash, red bumps on the legs, fever, soreness of the eyes, and pain and swelling of the ankles.
- Seizures, poor performance in school, facial paralysis, double vision and headaches. Showing growth failure, diabetes insipidus (excessive urination), and lack of sexual maturation.
- Sunlight can aggravate all the symptoms.

#### **Sarcoidosis diagnosis:**

- Angiotensin-converting enzyme (A.C.E) level, which are elevated.
- A biopsy of affected organ can be done to confirm the diagnosis,
- Kveim Test, a reaction appearing 4 wk after intradermal injection of sarcoid spleen or lymph node extracts, is positive in 50 to 60% of individuals.

- Calcium levels should be done as they are elevated especially during attacks.
- MRI/CT/Gallium scans & bronchoscopy are all possible during the diagnosis procedure.

### **Treatment for sarcoidosis**

- Commonly used treatments include corticosteroids like **Prednisone**, and immunosuppressive drugs such as Methotrexate, Cyclosporine and Hydroxychloroquine. A good starting dose of prednisone is 10 to 20 mg/day. If a prompt effect is desired then Prednisone 40 mg/day or methylprednisolone 48 mg/day is used, but such doses are poorly tolerated by many individuals.
- Those individuals who cannot tolerate prednisone need a trial of methotrexate starting at 2.5 mg/wk and increasing in increments of 2.5 mg/wk to a total of 10 to 20 mg/wk as tolerated by a WBC > 4000/mm<sup>3</sup>. After 8 wk of methotrexate, the corticosteroid can be reduced and then often discontinued. Serial blood counts and liver enzyme tests should be performed every 6 wk.
- Hydroxychloroquine 200 mg bid is more effective than corticosteroids for treatment of disfiguring skin. Ketoconazole an antifungal is useful in long term treatment especially if the calcium levels are elevated at a dose of 600-800mg.
- The inhaled steroids may help suppress active lung sarcoid while causing few if any side effects.
- Minocycline 200mg at least three times a week long term clears up skin lesions.
- Methotrexate at 12.5 mg to 20 mg per week for at least 6 months also helps in clearing up the skin lesions.
- Angiotensin Receptor Blocker can be used to reduce sensitivity to sunlight and to help people return to a normal lifestyle. (COZAAR).
- Removing vitamin D from food products helps. Particularly check the labeling on milk, breakfast cereals, diet supplements and vitamin preparations. Natural medications can also be a significant source of Vitamin D, and, in the absence of a reliable list of ingredients, such medications should be discontinued. Once all Vitamin D has been removed from the diet, sunlight remains as the major catalyst leading to the proliferation of sarcoid granuloma.
- The individual should wear sunglasses in all but the darkest of indoor environments. If there is a need to venture outdoors then thick clothing must cover all exposed skin, mandating the use of gloves and hats, and dark sunglasses. The individual should be instructed to stay indoors for the duration of any therapy aimed at inducing remission.

**Amyloidosis:** Amyloidosis is a disease that occurs when substances called amyloid proteins build up in body's organs. Amyloid is an abnormal protein produced by B cells bone marrow that can be deposited in any tissue or organ. Amyloid is an inflammatory disease and has been reported as a low grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type. Amyloidosis frequently affects the brain heart, kidneys, liver, spleen, nerves and gastrointestinal tract. Amyloidosis occurs in many autoimmune



diseases including SLE, arthritis, myeloma and people on dialysis. Usually seen in men over the age of 40.

The most common type of the disease, primary systemic amyloidosis, is a bone marrow disorder. Other types that come from the liver are considered familial, or inherited. In still other cases, amyloidosis may occur as a result of kidney disease in people who have undergone long-term dialysis therapy.

**Symptoms:**

- Severe fatigue, Weakness
- Weight loss, Difficulty swallowing, Diarrhea
- Shortness of breath
- Numbness or tingling in hands or feet
- An enlarged tongue (macroglossia)
- Skin changes
- Swelling of ankles and legs
- An irregular heartbeat

**Tests:** Blood or urine tests may detect an abnormal high protein levels. Rectal biopsy by a needle to remove a small sample of tissue

**Treatment:**

- Rituximab was given to act on B-cells, interfering with their production of autoantibodies. In individuals with amyloidosis, Rituximab was given to kill progenitor B-cells of the small clone terminating in amyloid-producing plasma cells.
- **Peripheral blood stem cell transplantation.** Peripheral blood stem cell transplantation involves using high-dose chemotherapy and transfusion of previously collected immature blood cells (stem cells) to replace diseased or damaged marrow. These cells may be your own (autologous transplant) or from a donor (allogeneic transplant). Autologous transplant is currently the preferred standard.
- **Medicines.** Therapies include melphalan (Alkeran), an agent also used to treat certain types of cancer, and prednisone, a corticosteroid used for its anti-inflammatory effects. Other types of chemotherapy regimens melphalan with high-dose dexamethasone or VAD, which stands for vincristine, Adriamycin and Dexamethasone are used.

**Interstitial lung disease (ILD),** Bronchiolitis obliterans and organizing pneumonia (BOOP). Diffuse alveolar damage (DAD) adult respiratory distress syndrome (ARDS)

Interstitial lung disease (ILD) comprises more than 200 disorders characterized by diffuse inflammation and **scarring** of the lung. Air is supplied to the lungs by the wind pipe called trachea which divides into smaller air pipes, the most tiny air pipe is called a bronchiole

which takes air to the tiny air sacs called alveoli. The lung has millions of these tiny air sacs (alveoli). The tissue between the air sacs of the lungs is called the interstitium. In ILD there is inflammation in the walls of alveoli and loss of alveolar blood flow due to inflammation in the tiny blood vessels called (capillaries). Inflammation in these parts of the lung may heal or may lead to permanent **scarring** of the lung tissue. Once **scarring** of the lung tissue develops, the condition is called **pulmonary fibrosis**. Fibrosis and scarring, in the lung tissue, causes permanent loss, of that tissues ability to transport oxygen. The walls of the bronchioles (small airways) also get inflamed, it is called bronchiolitis. Some of these autoimmune lung diseases have different names. Diffuse alveolar damage (DAD), adult respiratory distress syndrome (ARDS). The progression of these diseases is through stages named (exudative, proliferative, and fibrotic) that correlate with the time rather than its specific cause. Except for asthma all these diseases cause fibrosis. ILD is a clinical challenge because the disease spectrum can range from mild disease that is responsive to medications to progressive loss of pulmonary function and death. Corticosteroids and cyclophosphamide result in clinical improvement in a subset of individuals. The names of some of these diseases are:

- Usual interstitial pneumonitis (UIP), Nonspecific interstitial pneumonitis (NSIP)
- Bronchiolitis obliterans-organizing pneumonia (BOOP)
- Respiratory bronchiolitis associated interstitial lung disease (RB-ILD)
- Desquamative interstitial pneumonitis (desquamative IP)
- Lymphocytic interstitial pneumonitis (LIP)
- Acute interstitial pneumonitis, Farmer's lung, Honeycomb lung
- Acute interstitial pneumonia (Hamman-Rich syndrome, idiopathic ARDS)
- Alveolar proteinosis, pulmonary phospholipoproteinosis
- Asbestosis, Berylliosis, Hard-metal pneumoconiosis
- Coal worker's pneumoconiosis (black lung disease)
- Connective tissue disease-associated interstitial lung disease
- Desquamative interstitial pneumonia (DIP), Hypersensitivity pneumonitis (HSP)
- Systemic lupus erythematosus (lupus lung), Mixed connective tissue disease
- Lymphocytic interstitial pneumonia (LIP)
- Nonspecific interstitial pneumonia (NSIP)
- Pigeon breeder's disease , Pulmonary alveolar microlithiasis
- Eosinophilic granuloma (EG), histiocytosis X (HX), or Langerhans granulomatosis
- Pulmonary fibrosis, Respiratory bronchiolitis
- Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)
- Rheumatoid lung, Sarcoidosis, Polymyositis, Dermatomyositis, Scleroderma lung
- Silicosis, Pneumoconiosis ,Smoker's bronchiolitis
- Usual interstitial pneumonia (UIP) and IgA deficiency triggered ILD

**The causes** of these diseases are diverse from particularly those that involve mining or that expose workers to asbestos or metal dusts can cause pulmonary fibrosis. Workers doing these kinds of jobs may inhale small particles (like silica dusts or asbestos fibers) that can damage the lungs, especially the small airways and air sacs, and cause **scarring** (fibrosis). Agricultural workers also can be affected by exposure to organic substances, such as mold, hay, fumes and chemicals. Exposure to radiation can trigger these diseases and almost any

medication used can cause ILD except for aspirin.

**Symptoms of ILD:**

- Shortness of breath (dyspnea) on exercise, cough and fatigue.
- Dry rales ("Velcro" crackles) may be present on chest auscultation.
- Wheezing is not seen. **UNCOMMON**
- Signs of advanced disease include increased dyspnea and a fast heart rate (tachypnea), blue color of the skin (cyanosis) and digital clubbing.
- Advanced disease in children may result in weight loss or failure to thrive.

**Tests for ILD:**

- CT scan can determine the type of ILD present.
- Pulmonary Function Tests, the breathing test results are abnormal in ILD. Arterial Blood Gas: test measures the amount of oxygen and carbon dioxide in the blood. The results may be normal or show a reduced oxygen level.
- Bronchoscopy involves inserting a tube through the nose into the trachea (windpipe) to see the airways. In bronchoalveolar lavage, a small amount of sterile saline is placed in one area of the lung and then withdrawn. This fluid contains cells that will be analyzed under the microscope. People with chronic obstructive pulmonary disease have very high titers of antibodies to chlamydia, showing infection with that germ and anti-Ro/SSA antibodies are also seen frequently.

**IgG levels and IgG sub-class levels need to be done on all individuals.**

**Treatment for ILD:**

- Corticosteroids have emerged as primary pharmacologic therapy. Steroids have been used with varying degrees of success to treat ILD hypersensitivity pneumonitis and other forms of ILD. About 50% of individuals have responded to steroids Both oral steroids and pulse therapy have been used.
- Hydroxychloroquine is used in ILD, especially in pediatric individuals, because of its relatively low toxicity. Among cytotoxic agents, cyclophosphamide, azathioprine and methotrexate are used most frequently. Although cyclophosphamide is often the drug of choice as adjunctive therapy to corticosteroids in adults, a higher than expected sterility rate limits its usefulness in children.
- Intravenous pulse cyclophosphamide 10-30 mg/kg every 3-4 weeks, and 2-4 mg/kg/day of cyclosporine-A is also used for a complete list of drugs and side effects see the treatment section of CIDP.
- For individuals with low IgG levels or low IgG-subclass levels use - IVIg at 200mg/kg/month to 400mg/kg/month for four months to two years as needed.
- Lung transplant is to be avoided as the disease can develop in the transplant tissue.

## **Chapter 18 Renal autoimmune Disorders**

**Autoimmune Interstitial Cystitis:** Interstitial cystitis (IC) is a condition that results in recurring discomfort or pain in the urinary-bladder and the surrounding pelvic region. IC is

often associated with diseases such as allergies, irritable bowel syndrome, fibromyalgia, inflammatory bowel disease (Crohn's disease and ulcerative colitis), systemic lupus erythematosus, and Sjogren's syndrome (dry eyes). The symptoms vary from case to case and even in the same individual. People may experience mild discomfort, pressure, tenderness, or intense pain in the bladder and pelvic area. The prevalence of allergies in IC is reported to be between 40 and 80% of individuals. Usually the symptoms follow a remitting and relapsing course. Interstitial Cystitis individuals are wrongly treated for what their doctors assume must be bladder infections, urethritis, or "emotional" problems. Repeated symptoms of pain and urgency, suggesting a urinary tract infection, are a hallmark of IC.

### **Symptoms**

- Bladder spasms which are very painful, bladder frequency, bladder pain, low bladder capacity, and incontinence.
- (Urgency), a frequent need to urinate or (frequency),
- While urinating very little urine may be passed.
- Women's symptoms often get worse during menstruation. Rarely painful menstruation or pain during intercourse is reported.

**Test: Check CRP** to see if it is elevated. ANA antibodies may be positive; **urine analysis does not show a infection** but inflammatory cells are seen.

### **Treatment:**

- Doxycycline 100 mg twice a day taken on daily for 3 weeks a week has been reported to help in controlling the symptoms of IC. Both partners have to be treated or the treatment will not work. It has been shown that in individuals suffering from Cystitis who have elevated CRP or other autoimmune diseases that a trial of prednisone be used to control IC.
- Alcohol, tomatoes, spices, chocolate, caffeine, citrus drinks, artificial sweeteners and acidic foods may irritate your bladder. That makes symptoms worse. Try removing these from your diet.
- Using a TENS ("transcutaneous electrical nerve stimulation) unit helps improve the blood flow to the bladder.

**Henoch-Schonlein purpura:** Henoch-Schonlein purpura (HSP) is the most common type of vasculitis (inflammation within the blood vessels) diagnosed in childhood and is rarely seen in adults. The main clinical manifestations of HSP include purpura (small blue spots over the skin), arthritis, abdominal pain, gastrointestinal bleeding, and **nephritis** (inflammation of the kidney). The symptoms are caused by inflammation of the blood vessels resulting from IgA -antibody deposits in blood vessel walls. The mean age of

children affected by HSP is 5 years, and majority of children affected with HSP are younger than ten years old. HSP is most common from September to January and frequently follows a sinus infection. It has been attributed to pharyngitis caused by Streptococcus, hepatitis B infection, varicella, mycoplasma, herpes simplex virus, **Helicobacter pylori**, human parvovirus B19, and Coxsackie virus. H-pylori antibodies have been reported in HSP individuals frequently. Higher levels of H-Pylori antibodies are seen during new attacks of HSP. In a study new attacks of HSP were treated by 1mg/kg/day of prednisone for two weeks. In about 84 individuals none ever had any kidney involvement later on. HSP is generally benign and self-limited condition seen in children; and more severe in adults.

**Diagnosis:** Urine and blood test may show elevated CRP, Elevated BUN (Blood urea nitrogen), Serum IgA is often elevated.

**Treatment:** Prednisone 1mg/kg/day for two weeks. NSAID can be used if needed. The condition is self limiting and repeat attacks are usually not seen. We recommend you to follow the diet guidelines in the diet section. For adults please see the treatment guidelines below in autoimmune glomerulonephritis.

**Glomerulonephritis Autoimmune:** Each kidney contains approximately one million miniature filtering units, called nephrons. Each of these is made up of a glomerulus, a collection of capillaries (tiny blood vessels) that filters the blood. Inflammation of these filtration units is termed glomerulonephritis (GN). When GN develops as a long term condition, it is associated with an autoimmune reaction. This is where the body attacks these filtering units, in the kidneys. In such cases, symptoms of renal failure appear gradually over time. Injury to the abdomen or back may be triggering these diseases. Steroids given at the time of injury may prevent the development of these conditions. There are several types of GN but treatment is the same. It can be associated with hepatitis-C virus.

**Symptoms:**

- Feeling of tiredness, shortness of breath, a loss of appetite and high blood pressure.
- Fluid retention causes swollen feet and puffiness of the face and around the eyes.
- Urine is passed less frequently and may appear frothy, cloudy or blood-stained and dark in color.

**Diagnosis:** Urine and blood tests show elevated ESR, serum creatinine is elevated, MRI scan of the kidney shows enlargement of the kidneys and occasionally a kidney biopsy, may also be performed to establish the diagnosis and the severity of the problem. Serum C-reactive proteins levels are elevated, antineutrophil cytoplasmic antibodies (ANCA) are usually present. Antibodies against hepatitis-C virus need to be measured.

**Treatment:** If the inflammation is only mild, treatment with **doxycycline 200 mg once a day can decrease protein in the urine** it acts as a metalloproteinase inhibitor in glomerulonephritis. More severe cases may require a combination of antibiotics, corticosteroids and immunosuppressant drugs.

- If Hepatitis –C virus is found then treatment with interferon- $\alpha$  (3 million units subcutaneously, 3 times per week) and ribavirin (500 mg orally, twice a day) for 48 weeks is recommended which may resolve the GN.
- For rapidly progressive glomerulonephritis individuals IVIg is used at a dose of 400mg/kg for 5 days. Based upon tests can be repeated once every 4 weeks. The repeat dose is usually 400mg/kg single infusion only.
- For a complete list of drugs please see the treatment section under CIDP, fish oil supplements are useful in IgA type nephropathy..

**Chronic Autoimmune Prostatitis (CAP), Nonbacterial Prostatitis, Chronic Pelvic Pain Syndrome:** Prostatitis is common autoimmune inflammation that affects prostate gland in men around ages 19-91. The prostate is a gland that lies just below a man's urinary bladder. It surrounds the urethra like a donut and is in front of the rectum. The urethra is the tube that carries urine out of the bladder, through the penis and out of the body. The prostate gland makes a fluid that provides nutrients for sperms. This fluid makes up most of the ejaculate fluid.

Prostatitis can cause diverse symptoms. Urination becomes difficult and painful. You have to urinate more often. Some have a feeling of a fever, low-back pain or pain in your groin (the area where the legs meet your body). It may make you less interested in having sex or unable to get an erection or keep it. Prostatitis is easy to confuse with other infections in the urinary tract.

It has been reported that more than 90 percent of men with prostatitis meet the criteria for chronic autoimmune prostatitis and chronic pelvic pain syndrome. In a study using a needle biopsy for culture of prostate tissue, it was found that there is frequently an occult bacterial prostatitis, especially in men with leukocytes in prostatic secretions. Some studies have noted increased uric acid levels in prostate secretions in men with chronic autoimmune prostatitis. Benign prostatic hypertrophy is essentially a inflammation causing swelling and in reality is C.A.P. The cause of prostate cancer is chronic inflammation, which can easily be prevented by proper anti-inflammatory treatment.

**Symptoms:**

- Painful ejaculation or pain in the penis, testicles or scrotum.
- Low back pain, rectal pain, and pain along the inner aspects of the thighs.
- Irritative or obstructive urinary symptoms and decreased sex drive or impotence.
- These individuals do not have recurrent urinary tract infections.
- Individuals may have a tender prostate.

**Tests for CAP:** No bacteria will grow on any culture, but leukocytes may be found in the prostatic secretions. Urine cultures are negative after prostate massage. The pre-massage urine has fewer than 10 white blood cells per high-power field, and the post-massage urine contains more than 10 to 20 white blood cells per high-power field. PSA (prostate specific

antigen) can be checked in the blood can be elevated. ESR may be elevated, CRP may be elevated.

#### **The treatment for CAP:**

- Given the high rate of clandestine or hidden prostatic infections, **an antibiotic trial is reasonable**, to see if the individual responds clinically. *Chlamydia trachomatis*, *Ureaplasma urealyticum* and *Mycoplasma hominis* have been identified as potential pathogens, treatment should cover these organisms.
- Doxycycline (Vibramycin) 100mg/daily or minocycline (Minocin) 100mg/twice daily for 14 days, or erythromycin at 500 mg four times daily for 14 days.
- Hot sitz baths and nonsteroidal anti-inflammatory drugs (NSAIDs) may provide some symptom relief. Some men may notice aggravation of symptoms with intake of alcohol or spicy foods and, if so, should avoid them. In men with irritative voiding symptoms, anticholinergic agents such as oxybutynin (Ditropan) or alpha-blocking agents such as prazosin (Minipress), Hytrin may be beneficial.
- To achieve remission bolus therapy with cyclophosphamide and prednisolone is recommended. Please see dose guidelines in the CIDP treatment section.
- Bicycle seats are very important to prevent further injuries of the prostate. The most common bicycling associated urogenital problems are nerve entrapment syndromes presenting as genitalia numbness, which is reported in 50-91% of the cyclists, followed by erectile dysfunction reported in 13-24%. Other less common symptoms include prolonged erection (priapism), penile thrombosis, and infertility, blood in the urine (hematuria), and torsion of spermatic cord, prostatitis and elevated serum PSA. These can all be avoided by a flat seat, which does not have the nose.

**Wegener's involving the urinary tract (Orchitis-ureteral stenosis-pseudotumor of the bladder):** Wegener granulomatosis (WG) can present with urinary system involvement. WG needs to be diagnosed and treated quickly. If proper anti-inflammatory treatment is not provided, then kidney failure and vasculitis can affect other organs very quickly. Usually middle aged men are the main targets. Past history of arthritis, skin rash, **runny nose** and asthma, helps to diagnose Wegeners disease. Rarely WG can cause a facial paralysis and sudden onset of hearing loss. Respiratory tract infections can trigger relapses in individuals with WG in remission. Studies have suggested that treatment with trimethoprim-sulfamethoxazole (Septra) may be beneficial in preventing relapses.

**Symptoms:** Acute urinary retention related to **prostatitis**, inflammation of the testicle (**orchitis**), difficulty in passing urine due to ureteral stenosis accompanied by pain in the penis, urine bladder pseudo-tumor (inflammation causing the appearance of a bladder tumor) and causing blood in the urine, with penile ulceration. Some people experience narrowing of the trachea. The symptoms can include voice change, hoarseness, shortness of breath, or cough. Fever and night sweats may occur. Fever may signal an infection, often of the upper respiratory tract.

- **Sinus involvement:** A common sign of the disease is almost constant runny nose or other cold symptoms that do not respond to treatment. A hole may develop in the cartilage of the nose, which may lead to collapse (called saddle-nose deformity). The eustachian tubes, which are important for normal ear function, may become blocked, causing hearing loss with a feeling of a blockage or fullness in the ear.
- **Lungs:** Cough, hemoptysis (coughing up blood), shortness of breath, and chest discomfort.
- **Musculoskeletal system:** Pain in the muscles and joints.
- **Eyes:** Symptoms in the eye include redness, burning, or pain. Double vision or reduced vision.
- Conjunctivitis (inflammation of the conjunctiva, or other layers of the eye)
- Swelling of the eye muscles or Myositis
- **Skin lesions:** Appearance of small red or purple raised areas or blister-like lesions, ulcers, or nodules.

**Test:** anti-neutrophil cytoplasm antibody (ANCA) is usually positive, biopsy of the bladder or skin lesions will show the vasculitis. ESR is elevated and CRP is elevated. Increased protein in the urine and serum creatinine is elevated.

**Treatment:** Early high-dose steroids accompanied by Cytoxan should be used as first-line therapy to avoid unnecessary surgery. Septra (Co-trimoxazole (800 mg of sulfamethoxazole and 160 mg of trimethoprim) given twice daily for 24 months to prevent relapses in individuals. For other drugs please see the CIDP treatment guidelines.

## **Chapter 19, What is IVIG (Intravenous Immunoglobulin)**

### **1. What is IVIG or Intravenous Immune Globulin?**

IVIg is a collection of antibodies consisting mainly of IgG (immunoglobulin-G) A plasma product formed by taking antibodies from about 20,000 donors and mixing them together. These have proven effective in several immune system disorders, including nearly all autoimmune conditions including CIDP and GBS. The sooner you can treat the individual the better the results. There is a short window of opportunity usually within the first 18 months after the diagnosis. Treatment with IVIg within the window period is likely to halt the progress of the disease.

After being exposed to toxins and poisonous chemicals including carbon monoxide the body's immune system may mount an attack on the body. This autoimmune attack can be halted by IVIG.

### **2. How does IVIG work?**

For immune deficiency where the body does not make enough antibodies, IVIG supplies them. For autoimmune disorders like GBS & CIDP, there is an abnormal antibody (autoantibody) being formed which is inactivated by IVIG.

Individuals with autoimmune disorders like CIDP are deficient in anti-idiotypic antibodies. IVIG supplies them. Anti-idiotypic antibodies are normal antibodies which are produced in the absence of any antigen. They are capable of inactivating many different types of antigens.

### **3. How long does it take for IVIG treatment to have an effect?**



Individuals may see a response in 24- 48 hours. Some individuals will have to wait 3-4 weeks to see an effect. In a few no effects may be seen. If 4-5 cycles of IVIg do not show any response then doctors may try a different approach like plasmapheresis, cytotoxic or immune suppressants. Everyone is slightly different as it depends on how long has the disease process been going on. The sooner one treats it the faster the response.

#### **4. Why is IVIG so expensive?**

The plasma donors are paid then the plasma is sent to processing centers for mixing, antibody removal, chemical treatment and filtration to remove viruses. This is followed by the products to be freeze dried. All this ends up for IVIG to be priced at \$ 48 to \$ 58 a gram. A single infusion costs about \$3000 for a adult. For a child the cost is lower as a small dose is used.

#### **5. How is IVIG administered?**

IVIG is mixed in a bag and a tube runs from it to a vein usually in the arm. The recommended way to infuse includes a pump. Usually it is given at a rate of 100 cc/ hour to 200 cc/ hour. The rate is reduced for any problems such as headaches, rash, fatigue, hypertension or hypotension. For an adult's infusion is usually given over 5 to 6 hours.

#### **6. What are the common side effects OF IVIG?**

Some times individuals get a headache which is more common in females with a history of Migraines. Individuals may experience fatigue similar to getting Flu, which is due to antibodies interaction. Some individuals get a rash and doctors recommended they take Benadryl or even steroids to avoid this. Remember there are lots of antibodies and some may result in odd reactions. A severe headache with a stiff neck after IVIg may be due to aseptic meningitis. Variation in blood pressure, shortness of breath can also be seen.

#### **7. How can one reduce the side effects of IVIG?**

Remember to drink eight glasses of water a day for hydration before starting the treatment and continuing this a month after the last infusion. Some doctors recommend taking a baby aspirin to prevent thrombophlebitis. Individuals need to check with their doctors if they can use aspirin and should not take this if they are on coumadine or have bleeding disorders. Individuals should not take aspirin, if they have a history of gastric ulcers. Doctors use Premedication to help reduce side effects. Some recommend that one should take Tylenol or other NSAID for prevention of headaches and pains. Use a benadryl capsule for a skin rash and this will help you to relax during the treatment. Using low dose prednisone will reduce side effects like headaches.

#### **8. Where is the IVIG treatment given?**

IVIG can be given at home, in a doctors clinic or a hospital. Some individuals have even taken this at work.

#### **9. What is the frequency of the IVIG treatment given?**

Usually a dose of 2 grams per kilogram is divided into four doses and 500mg/kg is infused daily for 4 days. This is followed by a monthly infusion of 500mg/kg. Individuals who have side effects can take the treatment on alternate days. It is recommended that young women take this on alternate days.

#### **10. What are the differences in brands of IVIG?**

Generally the difference is in the amount of IgA content and whether the IVIg contains sucrose, glucose or some other sugar as a stabiliser. Some IVIg products have Glycine while another one has no preservatives. In general all the IVIg products work about the same.

**11. What is a recall OF IVIG?**

A recall happens when someone reports defects, side effects of a particular batch. Then the FDA may issue a warning or a recall. This may also depend on contamination.

A recall may be followed by shortage of the product in the market. Recently consumer demand for IVIg is surpassing production.

**12. Where can I find out about recalls of IVIG?**

The FDA in the US maintains a current list of blood-product recalls on its site. This is because its members use so many different types of blood products, and generally store them in quantity. Look under Biologics and then recalls near the middle of page.

<http://www.fda.gov/cber/recalls.htm>

**13. Who is a good provider for IVIG?**

Choose someone who knows about IVIG. Who has 10 years of experience with IVIg.

**14. What is the recommended dose as compared to age?**

Children can tolerate a higher dose and the whole 3g/kg dose has been given without side effects as a single infusion. Young adults up to 25 years of age can tolerate 1g/kg as a single infusion. Up to age 50 only 400mg /kg is recommended in one day.

When dealing with above 70 year old individuals we recommend not to infuse more than 400mg/kg in one week.

**15. What is the right IVIG product for me?**

Individuals with congestive heart failure or compromised renal function may fare better if they receive a product with a low osmolality and low volume; Individuals who are diabetic should receive a product containing no sugars; Individuals receiving products with sucrose may be at a higher risk for renal failure; Individuals with immunoglobulin A (IgA) deficiencies should only receive products with the lowest amount of IgA or they could have anaphylactic reactions. Individuals with small peripheral vascular access or a tendency toward phlebitis may want to avoid preparations with a low pH.

**16. I have no more veins left. How can I get IVIg?**

IVIg can be delivered by the subcutaneous route if venous access is a problem. This is the preferred way of delivery for a immune deficient individual.

**17. IVIG and vaccination issue.**

IVIg prevents vaccinations to take any effect in your body.

Immunizations should not be given for at least 1 month before -- and preferably 3 months after a course of IVIG. While on IVIg you may not need routine flu shots, as you are getting the antibodies from the IVIg.

**18. IVIg and blood tests:**

The ESR will usually go up after an IVIg treatment in the range of 80mm-100mm/hour. This elevation is considered normal following IVIg infusion.

**Chapter 20- How to take care of pain and stiffness:** Pain and stiffness are one of the most common problems in individuals suffering from autoimmune diseases. These symptoms are seen in nearly all autoimmune diseases and specially Fibromyalgia and Stiff Person Syndrome. Stiffness begins secondary to stress, exposure to cold, vitamin deficiencies and poor posture. Repeatedly doing the same task will also cause stiffness, lifting of heavy weights without stretching will result in stiffness. We have seen how a cat stretches after it gets up. That is what all of us need to do every morning. Stretching helps

reduce stiffness. Children cry at night because they are getting stiff due to the cold. Thus need an extra cover. Sitting in front of a air conditioner or cold air draft will cause stiffness. Stretching is very important and if you cannot lift your arm ask someone to help you stretch. In a few days you will be able to do this yourself.

Remember to take a hot shower after wakening up to reduce stiffness. Heat helps to relax the muscles. If the muscles remain stiff a short massage is helpful. Massage will reduce inflammation if done correctly. The painful deep massages increases inflammation and should be avoided.

Correct the vitamin deficiencies like B-12 Cynocobalamine, B-1 (Thiamine), and B-6 (Pyridoxine). Too much pyridoxine is toxic to the human nerves and thus should not be taken in large doses. In any person with chronic stiffness, calcium, magnesium, iron, thyroid functions and the vitamin levels need to be. If any of the hormone, mineral or vitamin levels are low then the treatments will not work.

I.V.I.g reduces stiffness as seen in the treatment of stiff person syndrome. Colostrum is the milk secreted after the delivery of a baby. Bovine colostrum taken at a dose of 500mg to 1000mg twice a day will also reduce stiffness. As stiffness is reduced then the pains go away. One becomes more active and feels youthful. We recommend that anyone with stiffness should use colostrum. Muscles become soft without any stretching, muscles spasms also become less.

For stiffness and pain in the body use a icepack rub it on the painful area then stretch that area by moving your extremities. This is followed by applying a hot towel on the same area, (moisten a towel with hot water and apply it over the stiff area).

In acute injuries seen in athletes require quicker treatments, in such situations a simple injection of lidocaine or just a needle insertion will relive the pain. This procedure can be done on any muscle in the body. Usually one milliliter (ml) or 1 cubic centimeter (cc) of lidocaine is injected into the painfull area, followed by stretching of the muscle for pain relief. This is a quick way to relive headaches and joint pains. If the lidocaine injection is not available just rub lidocaine or find a cream containing camphor/menthol combination, rub the cream over the painfull area to relive pain.

Myofacial pain syndrome is defined by the presence of trigger points. Trigger points are located within taut bands of muscle, whereas tender points are not. Palpation of trigger points often reproduces the pain radiation pattern experienced by the individual and can elicit a twitch in the muscle. The pain elicited on palpation of a tender point is localized to the area under palpation and does not elicit a jump or twitch. Lastly, trigger points often have a nodular texture described as similar to rubber, whereas tender points cannot be palpated.

Myofascial pain syndrome is a commonest cause of pain all over the world. This pain will cause tightness in the muscle, and the muscle loses its stretch reflex. If the trigger point in the affected area of the muscle is inactivated by a lidocaine injection, the muscle reflex will return instantly. To complicate the situation, Myofascial pain syndrome may occur in individuals with fibromyalgia. The pain of fibromyalgia is widespread, and associated with tender areas. Myofascial pain arises from trigger points in individual muscles, which can be felt like a small bump under the skin. Individuals refer to them as knots universally in America and U.K. The diagnosis of Myofascial pain syndrome should be considered when, by history, the individual's pain pattern is limited to a particular region over time.

One cubic centimeter of lidocaine injected into a trigger point or tender point will relieve pain. Sometimes a few repeated injections are needed. Some physicians use B-12 with B-6 and prednisone which provides long term relief. Not more than 10 cc of lidocaine should be given in one setting as chances of arrhythmia tend to increase when a dose of 10- 20 cc is given. When giving trigger points make sure the person has normal B6, B-12 levels or the injection may not work. We have seen individuals with severe knee arthritis who came to the clinic in a wheel chair. After the trigger point injection they walked out of the clinic. If spasticity is causing a problem then Botox can be injected in the affected muscle, to relieve spasms for a few months.

Usually heavy lifting, repeated exercises, poor eating habits (less fat in the meals) will cause muscle spasms. Proper nutrition combined with muscle stretches should make muscle pain a thing of the past.

Muscle stimulators and TENs unit work wonders for chronic pain and stiffness, including stiffness in the chest, abdomen and urinary bladder.

## **Chapter 21-Getting around managed care.**

Every insurance company and state funded plans in western countries follow similar health guidelines. FDA guidelines are global and followed all over the world.

I.V.I.g. is approved by FDA for immune deficiencies and two autoimmune diseases which are thrombocytopenia and Kawasaki disease. I.V.I.g is not FDA approved for the treatment of any other autoimmune disease. If an insurance carrier denies you of I.V.I.g treatment saying it is not F.D.A. approved for M.S., G.B.S. or C.I.D.P. Then your answer should be that in fact I.V.I.g is off label approved by F.D.A and is also approved by the N.I.H.

If you have Fibromyalgia, Chronic fatigue or infertility you may be denied by the insurance company to obtain IVIg treatment. To get IVIg obtain some simple blood tests like IgG levels and IgG subclass levels, if they come out low then submit this information to the insurance carrier saying you have immune deficiency and that is an approved condition by the FDA for treatment with IVIg. Most cases get an approval right away.

Suppose you have SLE, arthritis or P.A.N.D.A.S or any other disorder including infertility and you need IVIg. You can get this approved by submitting it under the ICD9 code *autoimmune disorder unspecified*. With the submitting papers add an abnormal antibody level like ANA, Rheumatoid factor, raised A.S.O. titer and usually this will get approved.

If you need specific help, submit a question to [www.cidpusa.org](http://www.cidpusa.org)

**Disability how to get it:** This is mainly aimed at the United States Social Security and Disability Act (SSI). One has to remember that disability is a Legal issue and not a medical one. The person has to show why they cannot be employed in a regular job. The date of payments begins from the day you applied. Thus if it takes three years for you to get a approval and numerous application SSI will have to start reimbursements from the day you first applied.

The autoimmune diseases are invisible. Thus the doctor or judge cannot see them. So that is not a day to put a new suite on, wear your regular clothes. The person evaluating you will get an impression that you have some physical ailment. If you provide completes paperwork of your diagnosis, blood tests, doctors reports you will get the award sooner. So remember its the paper work that makes the difference. If they send you for evaluation to a doctor, go and explain all your problems. That is not a place to cry, unless you are trying to get a mental disability. Use a cane to walk it helps get sympathy.

It is helpful if your physician can provide a statement that in his opinion you are disabled from any gainful employment and this medical condition appears to be permanent. Attach your abnormal tests results and submit the package. If you get denied apply again most people get approved on the thirds or fourth attempt. The longer it takes to get disability the higher the payments, S.S.I. payments are calculated from the time you fist filed the application.

## **Chapter 22- M.M.M**

**MOLD:** We have tried to raise the awareness of Mold causing a autoimmune reaction and resulting in chronic sickness which can be simply treated with complete remission with proper medical help. Mold can be prevented. An environment with high humidity attracts mold and prevention from this becomes a key. Ventilation of areas that develop high humidity is important.

**Mold exposure.** The major presentations are headache, general debilitating severe pains, nose bleeding, fevers with body temperatures up to 40 degrees C (104 degrees F), cough, memory loss, depression, mood swings, sleep disturbances, anxiety, chronic fatigue, vertigo, dizziness, and in some cases, seizures. Although sleep is commonly considered a restorative process that is important for the proper functioning of the immune system, it could be disturbed by mycotoxins. Most likely, mycotoxins exert some rigorous effects on the circadian rhythmic processes resulting in sleep deprivation to which an acute and transient increase in NKC activity is observed. Depression, psychological stress, tissue injuries, malignancies, carcinogenesis, chronic fatigue syndrome, and experimental allergic

encephalomyelitis is induced at very low physiological concentrations by mycotoxin-induced NKC activity. Chronic exposures to toxigenic mold could lead to abnormal NKC activity with a wide range of neurological consequences, some of which were headache, general debilitating pains, fever, cough, memory loss, depression, mood swings, sleep disturbances, anxiety, chronic fatigue, and seizures. Yellow Rain which is a mixture of Mycotoxins and chemicals was used as a chemical-biological agent in Southeast Asia in the 1970's. Russia used Yellow Rain against Afghanistan and Southeast Asia. Yellow rain can be used to clear out an area of local people and within 24 hours occupying forces can move in to inhabit the area. Yellow Rain loses all toxic effects within 24 hours after being exposed to oxygen. Trichothecene mycotoxins are noted for their marked stability environmental conditions. On a weight-for-weight basis, they are less toxic than other toxins such as ricin, botulinum, and staphylococcal enterotoxin B, but trichothecene mycotoxins are proven lethal agents in warfare. Symptoms include vomiting, pain, weakness, dizziness, ataxia, blindness, anorexia, diarrhea, bleeding, skin redness, blistering, and gangrene, as well as shock and rapid death. Sensitive immunoassays and chemical procedures are available for the identification of trichothecene mycotoxins in biological samples.

**MSG syndrome:** Monosodium glutamate (MSG) syndrome occurs in response to free-glutamic acid, which is a breakdown product of protein after it has been processed by a food manufacturer. While all protein has glutamic acid bound in it, it is only the glutamic acid that has been freed from the protein before it is consumed that causes the reactions. Growing numbers of individuals and physicians and some scientists are convinced that the ingestion of this processed free-glutamic acid can cause adverse reactions in one or more organs of the body.

**Symptoms that MSG can bring on:** Reported MSG reactions, which can occur as a result of consuming even small amounts (much less than the 1/2 gram), include migraines; hives; mouth eruptions; numbness; tingling; swelling of mucous membranes in the oral, gastrointestinal or reproductive tract; asthma; runny nose; insomnia; seizures; mood swings; panic attacks; diarrhea; and cardiac irregularities.

MSG by any other name is just the same. "monopotassium glutamate," "autolyzed yeast," "hydrolyzed soy protein" and "sodium caseinate" are examples of ingredients that always contain MSG.

- In Japan, MSG is labeled as  
In China, MSG = Ajinomoto  
In the Phillipines, MSG = Vetsin  
In Thailand, MSG = phong churot  
In Germany, MSG = Natriumglutaminat  
In Europe - MSG = E621, but avoid E620-625 as they also contain glutamate

But how does MSG cause obesity? Like aspartame, MSG is an excitotoxin, a substance that overexcites neurons to the point of cell damage and, eventually, cell death. Humans lack a blood-brain barrier in the hypothalamus, which allows excitotoxins to enter the brain and cause damage, according to Dr. Russell L. Blaylock in his book *Excitotoxins*. According to animal studies, MSG creates a lesion in the hypothalamus that correlates with abnormal development, including obesity, short stature and sexual reproduction problems.

**Mad Cow:** Prof Alan Ebringer, an expert in auto-immune diseases at King's College, London, challenged the accepted mainstream scientific theory that CJD and BSE in cattle are caused by rogue "prion" proteins. His research suggested that BSE was caused instead by acinetobacter a common microbe in sewage and the soil.

He said it was this microbe, not the "prion" agent which was passed on to cattle in inadequately processed animal mixed with faeces contained in internal organs rendered as animal protein in "winter food" for livestock. Animal waste containing faeces was known in the trade as "green offals", he said. People could also be infected by this bacteria in the environment. "If we are right, the cattle kill was unnecessary," Prof Ebringer said.

Prof Ebringer and Prof John Pirt, a worldwide authority on the role of bacteria in diseases, said their work had shown that CJD and BSE could be caused in genetically susceptible people and animals when their own bodies produced fierce antibodies which then attacked the invading acinetobacter bacteria and damaged healthy tissue too. In effect, healthy tissue was destroyed by a heavy burst of "friendly fire" from the body's defence mechanisms.

Prof Ebringer and Prof Pirt from Kings College London rejected the prion protein theory championed by the Nobel prizewinner, Prof Stanley Prusiner, of California University, and generally accepted as the most likely cause of scrapie, BSE and CJD. They said that Prof Prusiner's theory which he will explain to the inquiry in June - was flawed. "The prion theory is not compatible with current concepts of molecular biology and postulates the existence of novel particles which cause neurological damage," they said in their statement to the inquiry. "The auto-immune theory is compatible with the current concept of molecular biology and proposes that BSE or scrapie are produced by a mechanism involving 'molecular mimicry' between common bacteria and nervous tissue." "Dismissing research showing how BSE could be caused by injecting infected brain tissue from cattle into other animals, they said the work was deeply flawed since none of the material used was "pure" BSE prion protein but a mixture including normal brain tissue. They argued that acinetobacter microbes in normal brain tissue caused similar brain damage to that attributed to the prion protein. By failing to separate the two ingredients, scientists had no way of proving that prion protein was to blame. They said: "It has been known for over 120 years that, if one injects brain tissue into another animal, a neurological disorder develops three to six weeks later and it is known as 'experimental allergic encephalomyelitis'." Some more research showed that the infected cows were being fed contaminated bone meal, which had caused Mad Cow crisis in UK. ( From UK news)

**Chapter 23-Joint- replacement & inflammation:** When an arthritic joint is removed, it is replaced with prosthesis an artificial joint typically made of a metal piece such as various alloys that fit closely into a sturdy plastic segment. These materials eventually erode, releasing tiny metal and plastic particles that enter the joint space. Some artificial joint recipients **experience chronic inflammation** as a result, leading to pain and loosening of the joint, which may require another replacement.

The inflammatory response results when the body senses a foreign intruder. One of the ways the immune system tries to eliminate the intruder is by calling in cells to fight. Everyone who receives a new joint has some inflammatory response, and everybody sheds tiny particles of the device into the joint space. Could inflammation be the reason why some people develop loosening while others do not.

The most common complication of hip replacement surgery is an inflammatory reaction to tiny particles that gradually wear off of the artificial joint surfaces and are absorbed by the surrounding tissues. The inflammation may trigger the immune cells to eat away some of the bone, causing the implant to loosen. To treat this complication, the doctor can use anti-inflammatory medications or recommend revision surgery (replacement of an artificial joint).

**Implants and autoimmune disease experts from medical reports:** Danish women with cosmetic breast implants experienced higher overall mortality compared with women in the general population owing in part to a 3-fold increase in suicide.

A group of 18 individuals had developed symptoms of their disease after they had received implants. Six had autoimmune disease (systemic lupus, 2 individuals; rheumatoid arthritis, 2 individuals; multiple sclerosis, 1 individual; and Raynaud's disease, 1 individual). Twelve had rheumatic disease (fibromyalgia, 10 individuals; inflammatory arthritis, 2 individuals). All 100 individuals were extensively evaluated pre- and postoperatively by interviews, clinical assessment, 45% of the 75 questionnaire responders felt that their implants had caused permanent health problems and 56% felt that they had not been given adequate informed consent by their original physicians. Studies show a association between extracapsular silicone from ruptured silicone breast implants and Fibromyalgia. If this association persists in other studies, women with silicone gel breast implants should be informed of the potential risk of developing fibromyalgia if their breast implants rupture and the silicone gel escapes the fibrous scar capsule. Women with silicone breast implants often report severe pain and chronic fatigue. Rupture of the implant is associated with an increase in symptoms of pain and chronic fatigue.

Autoimmune diseases have many causes. One mechanism by which infection is linked to the initiation of autoimmunity is termed molecular mimicry. Molecular mimicry describes the phenomenon of protein products from dissimilar genes sharing similar structures that elicit an



immune response to both self and microbial-proteins. Molecular mimicry is the mechanism by which infections trigger autoimmune diseases.

**Chlamydial:** Chlamydia infections are among the most common human infections. Every year, in millions of humans, they cause infections of the eyes, the respiratory tract, the genital tract, joints, and the vasculature. Chlamydia is intracellular resident so it is difficult to detect in blood samples. Chlamydia grows, in susceptible host cells that include mouth and vagina-epithelial cells, blood vessel-endothelial cells, heart muscle cells, and within monocytes and macrophages, reducing their survival while causing various autoimmune diseases. **Chlamydia infections often precede the initiation of autoimmune diseases and Chlamydia is often found within autoimmune lesions.** Chlamydia has been suspected in the etiology and pathogenesis of autoimmune diseases.

**Mycoplasma** is a microorganism which lack a cell wall can invade every human tissue and then they compromise the immune system, permitting opportunistic infections by other bacteria, viruses, fungi and yeast. *Mycoplasma*, *Chlamydia*, *Borrelia*, *Rickettsia* and other pathogens can also damage and kill nerve cells resulting in degeneration of the nervous system. Individuals with hidden infections, caused by mycoplasma, can be treated using antibiotics effective. Mycoplasma infections are usually difficult to detect. If the individual is suffering from the cold agglutinin syndrome then there is a simple blood test by taking a tube with EDTA in it, mix some of the individual's blood and place the tube on ice. If sand like particles form then cold agglutinins due to Mycoplasma are present. Once diagnosed, the Mycoplasma can be effectively treated, by using low dose Doxycycline. The treatment has to be long term, in selected cases. Double-blind clinical studies, sponsored by the National Institutes of Health, indicate that some antibiotics are effective in treating Rheumatoid Arthritis. Other, recent studies some by Garth L. Nicolson, show that in addition to Rheumatoid Arthritis, other autoimmune diseases, can be treated with antibiotics to suppress chronic bacterial infections, and antivirals to suppress chronic viral infections. Individuals with such infections gain significant benefits by undergoing therapies against chronic bacterial and viral infections.

### Acknowledgements

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**Due to space limitations we could not provide all the references on which the materials of this book are based upon. The vast majority of the materials our material comes from research studies at the National Library of Medicine in Washington DC.**

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