



# **Dizziness and Balance Disorders**



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# Dizziness and Balance Disorders

Studies indicate that “dizziness” is among the three most common complaints for patient’s to seek the help of a doctor, sharing equal time with headaches and low back pain. Approximately 11.3 million visits per year, or 5 to 10 percent of all office visits, are for the complaint of “dizziness”. A study by the National Institute of Health estimates that 40 percent of the population over the age of 40 will experience a “dizziness” disorder during their lifetime.

The symptom of “dizziness” can be described by patients from a variety of medical conditions. In general, “dizziness” is typically used to describe a sensation of lightheadedness, motion or a disturbance in stability. General descriptions of “dizziness” may include a sensation of “spinning, unsteadiness, lightheadedness, disorientation, imbalance, wooziness, visual difficulty, floating or a “drunk” feeling”. Your history will focus on the particular description and categorize your problem into 4 major categories to be investigated; the circulatory system (heart and blood pressure), the inner ear, the muscular system and/or the brain.

It is imperative to ensure that you are not suffering from a life-threatening condition. This typically consists of a work-up to assure that your circulatory system and brain are not the cause of your “dizzy” symptoms. Once your physician is comfortable that you are not having difficulty with these vital organs, then a more complete diagnostic investigation can be initiated.

**Vertigo** is defined as a sensation of movement and does not always involve a perception of spinning. In some patients the symptoms may be subtle and involve only a sensation of “swaying” or of an “inability to focus”. Some patients will experience movement of their surroundings or may feel like the ground is unstable. Sensations of vertigo typically are produced by an abnormality of the inner ear.

**Imbalance** is usually described as a sensation of unsteadiness. This may be related to long-standing damage of the inner ear or abnormalities in muscular strength or control. Patients with inner ear abnormalities will perceive the imbalance as “in their head”, while patients with muscular control problems or brain damage will have an inability to coordinate their movements and typically describe their imbalance as “in their feet”. Imbalanced patients are at high risk for falls and usually show signs of their balance difficulty. These signs may include bruises on their arms and legs from stumbling or a history of recent orthopedic injuries.

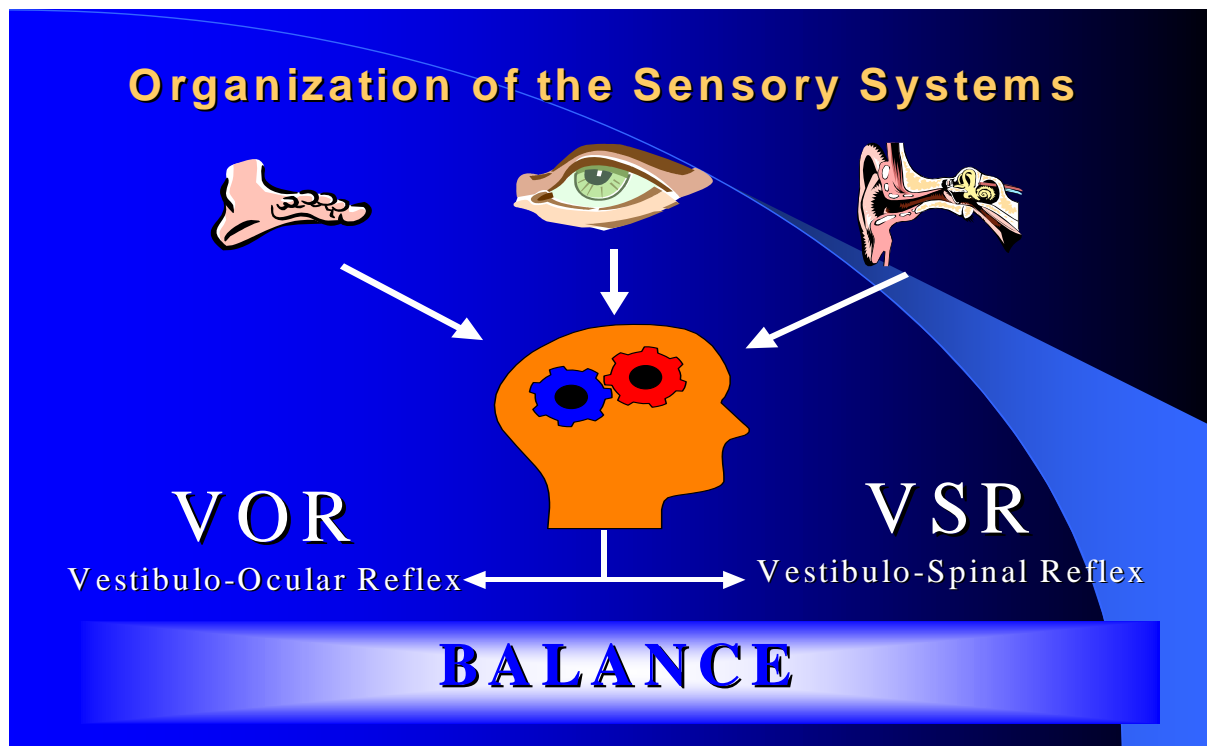
# Diagnosing the Problem

The most important part of each evaluation is the history of the problem. A detailed description of symptoms is the key element used in directing the appropriate tests required for diagnosis of the problem. Important questions which will likely be asked include:

- ◆ How often are you “dizzy” and how long does it last (seconds, minutes, hours, days)
- ◆ Do you have spells or are your symptoms constant
- ◆ Have you had blood pressure or heart problems in the past
- ◆ Do you have hearing loss, ringing or fullness of the ears, headache, severe allergies
- ◆ Do you get worse with changes in position, weather changes, mental stress, exertion
- ◆ Do you have difficulty maintaining your balance in the dark or on soft surfaces
- ◆ Do you have short term memory loss or a lack of concentration
- ◆ Have you had panic attacks or depression
- ◆ Is there a family history of vertigo, imbalance, tremor, Alzheimer’s, Parkinson’s, etc.
- ◆ Do you have a history of stroke, migraines, TIAs, seizures
- ◆ Have you fallen or nearly fallen recently
- ◆ Have you had any recent vaccinations
- ◆ Do you have a history of problems with insulin metabolism (Diabetes, hypoglycemia)

## How does the balance system work?

As we move through our environment, information is gathered from our vestibular (inner ear), visual (eyes) and somatosensory (neuromuscular) systems and sent to our brainstems for integration. This information is eventually transmitted to our brain cortex for perception and processing. “Dizziness” can result from disturbances of any of these systems or from an inability of the brain to process the information properly. Of all these, 85% of patients with complaints of dizziness have a vestibular (inner ear) abnormality.



## Where is the underlying problem?

Sensory abnormalities that create symptoms of dizziness and imbalance can be linked to abnormalities at three major locations in the sensory systems:

- **The sensor (inner ear, eyeball, etc)**
- **The nerves sending information to the brain**
- **The brains ability to process the information**

## Why can't anybody tell that I'm sick?

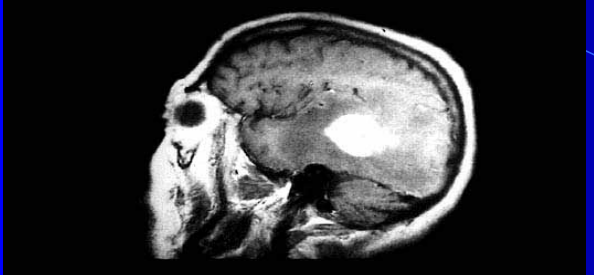
Perhaps the most confusing aspect of chronic dizziness or imbalance is the clinical presentation. Due to the multiple sensory systems involved in balance and the ability of the body to compensate, the patient with a pure inner ear abnormality of chronic nature does not typically appear ill to their doctor, friends or family. Only when a person with imbalance is challenged does it become apparent that they are even having a problem.

The inability to be recognized as ill often causes the patient to profess his/her abnormality to family, friends, co-workers and even strangers. Due to the inadequate treatments and therapies prescribed, many patients are typically labeled as "problem patients" by inexperienced doctors and their families. Commonly, patients feel they are, in effect, mentally and physically "disabled". They are often

viewed as being hypochondriacs, chronic complainers and are typically told that they may have a mental illness. Quite often, they are referred to psychiatrists and psychotherapists.

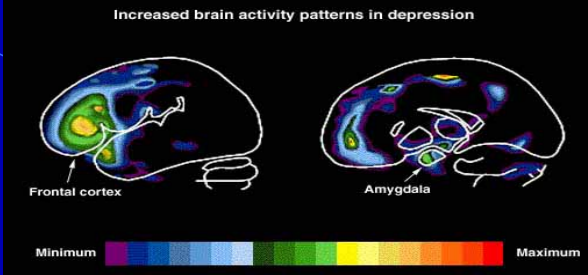
Neurological “symptoms” (such as dizziness, pain, tingling, numbness, tinnitus, etc.) are impossible for physicians to “see”. Imaging studies routinely used by physicians invariably are normal in most patients. Additionally, electrical brain studies rarely identify abnormalities in the “dizzy” patient. These facts routinely leave the physician using his “best guess” in treating neurological disorders including “dizziness”.

## Current State of Neurological Medicine



**MRI of Brain**


Beautiful Pictures  
No Functional Information



**PET of Brain**

Function Based  
Records response, not cause

**EEG of Brain**



Normal findings leaves the Physician treating symptoms by “best guess”

## SENSORY VIEW™

In our office, the **SENSORY-VIEW™** system incorporates the complete array of state-of-the-art, insurance approved diagnostic tests designed to measure the function and accuracy of the sensory information being delivered to your brain. This evaluation provides the most advanced diagnostic analysis of your sensory systems into a simple, seamless process that provides easy-to-interpret graphics. This process allows physicians to identify the extent of your medical problem and customize your individual treatment plan.



Using an advanced diagnostic algorithm of tests, the **SENSORY VIEW™** system will allow your physician to provide a specific diagnosis of your condition based on “objective” findings. The patient then is given a customized treatment program for their particular form of “dizziness” or imbalance. The customized treatment plan based on “objective” evidence is what produces our better-than-average outcomes and high patient satisfaction.

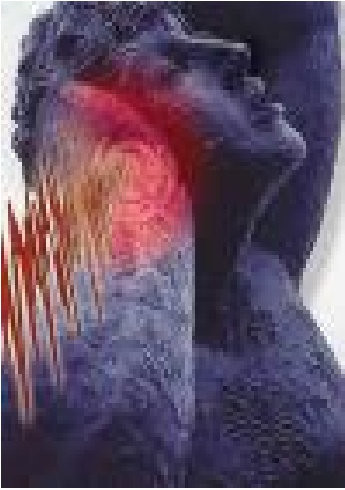
**The diagnostic evaluation of the balance disordered patient has three primary goals:**

- **Locating the source of the problem**
- **Assessing the severity of impairment and stability of function**
- **Determining if the abnormality appears reversible**

### **“I Don’t Have a Hearing Problem”**

Abnormal balance without some form of hearing abnormality is relatively rare. The hearing and balance systems of the inner ear are intimately integrated and function similarly. Evaluation of the hearing provides the physician with great insight into the cause or causes of your balance disorder. A study by the National Institute of Health estimates that 56% percent of the population over the age of 40 will experience a form of hearing disorder during their lifetime. The most frequent early symptoms of hearing loss are subtle in nature and include difficulty understanding in background noise, misinterpreting words, ringing or noise in the ear, fullness, muffling or complaints from the family. Many patients falsely believe it is only a condition of the elderly. Therefore, it is extremely important for doctor and patient to thoroughly discuss symptoms related to hearing in order to properly direct your diagnostic work-up.

## What is tinnitus?



Tinnitus, a symptom that commonly accompanies dizziness, is defined as the perception of noise in the ear without sound being present. This noise can be of any type: ringing, roaring, “crickets”, static or multiple pitches. Tinnitus is generally divided into two types: **central** or **peripheral**. Central tinnitus is generally believed to be created in the brain as a result of hearing loss. Peripheral tinnitus is caused by inflammation of the inner ear from chemical or infective origin and is much more common than central tinnitus.

## Other Associated Symptoms of Dizziness and Balance Disorders

Abnormal function of the inner ear is responsible for many symptoms caused by the brain attempting to adapt to the abnormal function. It is not uncommon for permanent damage to the balance system to result in long-term symptoms even after the first episode of dizziness. Most physicians fail to recognize the long-term symptoms that may accompany the balance-disordered patient. These symptoms are sometimes vague and most patients will appear “normal” at first impression. Commonly overlooked complaints include cognitive dysfunction, “short-term” memory loss, difficulty with concentration or “focus”, sleep pattern disruptions, anxiety, irritability, panic attacks and even depression. Although not life threatening, these symptoms alter the patient’s lifestyle and lead to social and work related difficulties. These symptoms are common to all patients with inner ear abnormalities; however, they are not routinely attributed to abnormal function of the balance system.

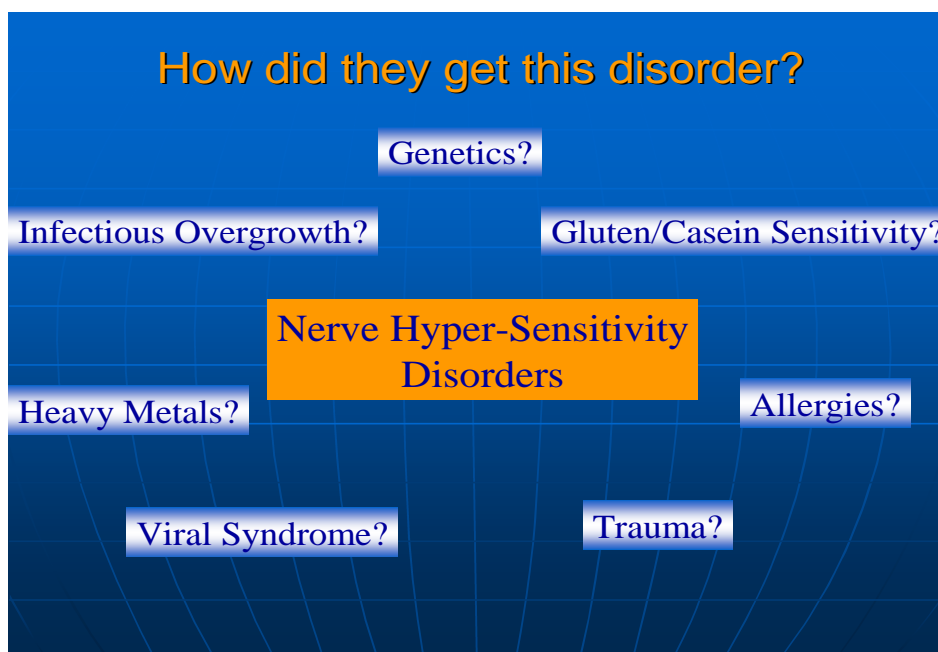
The **Reticular Activating System (RAS)** is an area of the brain that acts as the “processor” for incoming information of all types and is responsible for “awareness” or the feeling of being “awake” or “clear”. Abnormal input from the inner ear, causes the brain to slow the processing speed due to conflicting information regarding the body’s position in space. Slowing of the **RAS** causes sensations of “fogginess”, “fuzziness”, short-term memory loss, trouble focusing on “task”, an inability to concentrate and sleep pattern disruptions. This produces obvious difficulty for patients in the work environment and may be severe enough to cause poor job performance, poor job attendance or a relative “disability”.

The **Limbic System** is a portion of the brain responsible for sensations of “feelings”. Patients with balance abnormalities often describe sensations of hyper-emotionality typically describing uncontrolled outbursts of crying or emotion. Additionally, patients frequently describe sensations of panic, and may have frank panic attacks. Many patients have been given anti-depressants or benzodiazepenes (Valium, Xanax, Antivert) to assist them with these symptoms. These symptoms will not resolve until the brain is forced to compensate for the abnormal input it is receiving from the malfunctioning ear. Once the balance system has returned to normal, these symptoms will improve.

## Why is sleep so important?

Clinical research has been able to show a correlation between sleep abnormalities and inner ear abnormalities. This correlation is related to a lack of Stage IV sleep, commonly known as “deep sleep”. During Stage IV sleep the body produces a hormone called IGF-1 (Somatomedin-C). This hormone is required for proper transport of proteins, essential fatty acids and other nutrients into cells during their repair. A short-term deficiency of this hormone usually causes only one symptom; **fatigue**. If this deficiency persists, then patients are routinely labeled with **chronic fatigue** and may develop deficiencies of bone density, reduction in muscle strength, exercise intolerance, emotional lability, increased body fat and higher lipid and cholesterol concentrations in the blood. Fatigue is almost a universal complaint of all patients with nervous system abnormalities. Increasing the levels of IGF-1 in patients with deficiencies has been shown to alter the progression of neurological symptoms, decrease cholesterol levels, lower body fat, increase bone mineralization and reverse demyelinating processes.

## How did you get this disorder?



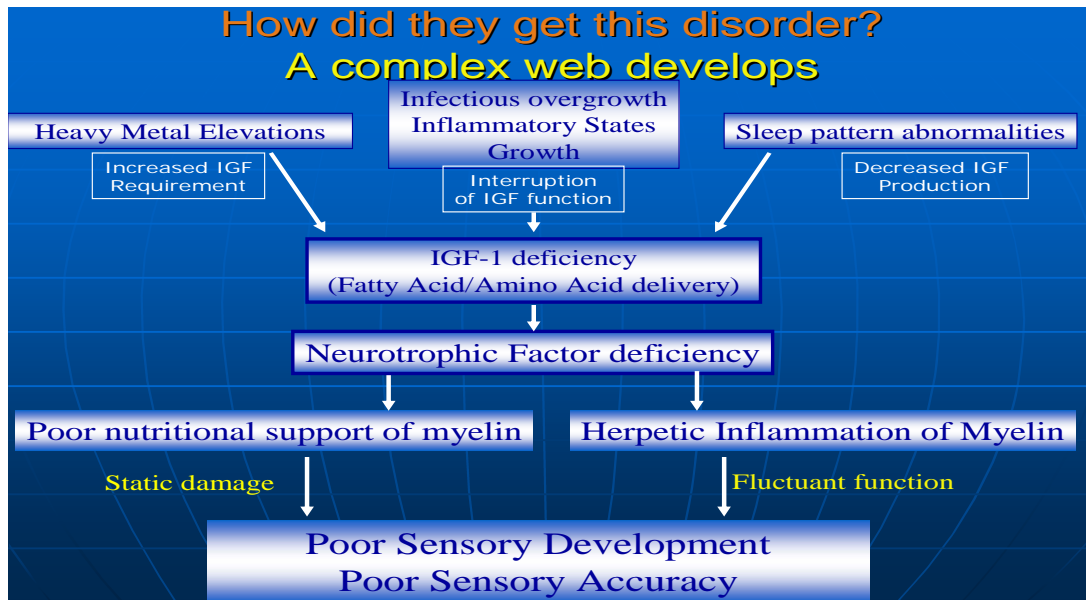


Review of the medical literature with regards to the “Nerve Hyper-Sensitivity” Syndromes presents a very confusing picture to most patients and professionals. A great deal of the literature focuses on allergies, heavy metals, secondary infections and enzyme abnormalities. It is important to realize that each of these problems are important and may be considered in each patient’s situation. It is equally important to realize that these disorders are nerve based problems that may have a multi-factorial origin and each patient must have a customized treatment plan unique to their needs.

NECA’s diagnostic protocol was developed using some common sense principles involving all nerve diseases. In adults, nerve diseases tend to be 1) deteriorative in nature (they get worse over time) and/or 2) fluctuant (have periods of worsening followed by periods of stability). Past experience with the nervous system disorders would dictate that this pattern can only be explained by continual exposure of a toxic agent or by an fluctuating infectious process. In nervous system disease this can only be attributed to three main culprits, elevated heavy metal concentrations, environmental toxins or neurotropic viral groups.

One could assume that this simple concept of nervous system disease should have been seen previously by experienced physicians, however, there is only one problem with proving this concept; the offending agents are difficult or impossible to quantify by blood or urine testing. Heavy metals are very difficult to quantify (measure) due to their ability to collect in “fatty” tissues. Much debate has centered on the best way to determine if heavy metal exposure or metabolism is an inherent problem. Additionally, many neurotropic viral groups (Herpes for instance) have no known method of quantification and titer testing is inconsistent.

NECA’s clinical methods are based on a clinical model that assumes that elevated heavy metal titers or viral overload initially interrupted sensory organ development or sensory nerve myelination. Following the initial interruption in sensory development, continued high heavy metal concentrations, infectious overgrowth and/or poor sleep patterns create an environment of IGF-1 depletion. Decreased IGF-1 activity appears to trigger continual activations of neurotropic (nerve infecting) viral agents cause fluctuating and frequent inflammation in the sensory organs or their nerves. This inflammation creates a fluctuating function or delivery of sensory information and relative conflict for the brain. The variability in the sensory system function does not allow the brain to integrate the different sensory systems and leads to a dynamic and confusing clinical state.



## Is there a way to reverse these disorders?

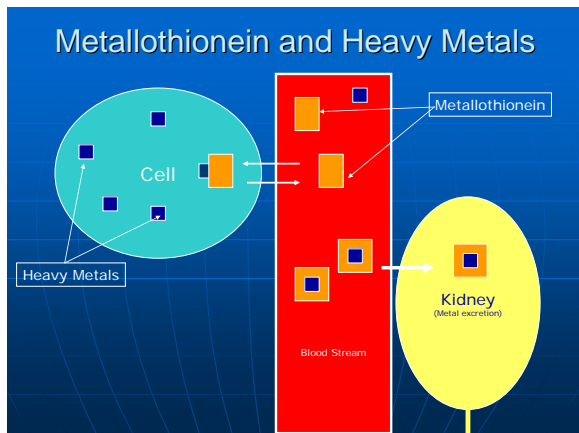
There appears to be four necessary clinical measures needed to ensure the greatest possibility of success in reversing neural disorders.

### Four necessary elements

1. Evaluate and reduce any heavy metal issue to erase toxic environment
2. Reduce viral load to eliminate inflammation of myelin
3. Reduce fungal/bacterial/allergic immune hyper-stimulation
4. Maximize hormonal and nutritional status to improve the repair of myelin

### 1. Evaluation of Heavy Metal Environment

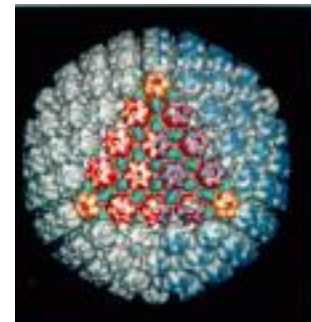
Recent advances in clarifying heavy metal metabolism in the body has revolved around the hormone Metallothionein. Metallothionein is a protein that binds to most heavy metals and allows them to be excreted from the body in the urine and sweat glands. This hormone is particularly important in clearing the “fat soluble” heavy metals such as lead, mercury, aluminum, cadmium and arsenic. Quantification of this hormone is now available and has indicated that many patients fall into a distinctive group of patients having lower than normal levels of Metallothionein. This condition will allow abnormally high concentrations of heavy metals to develop over time.

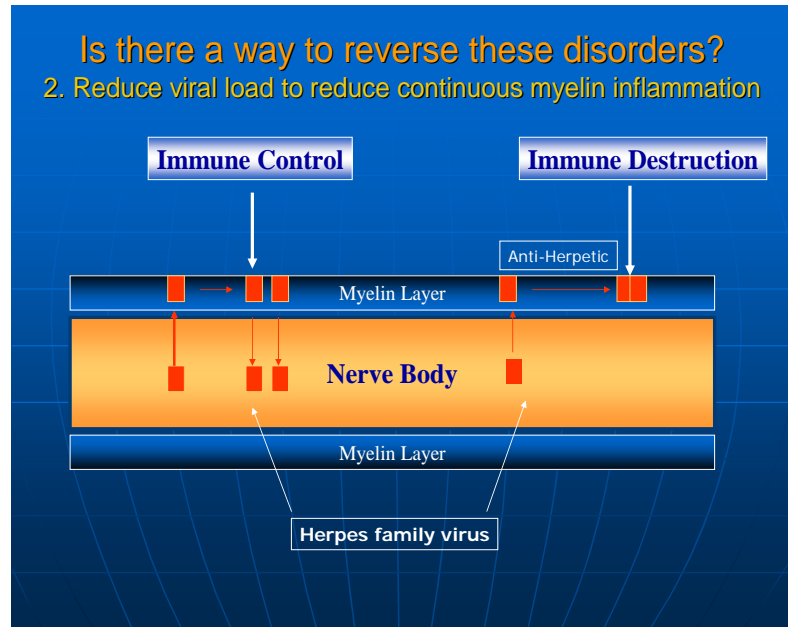
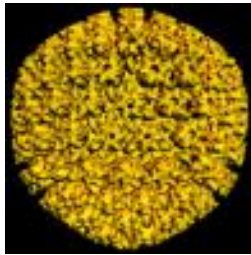
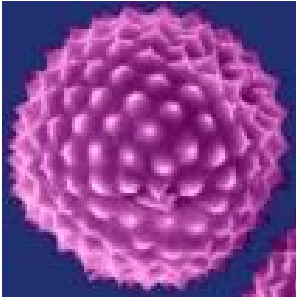


Elevated heavy metal concentrations have been shown to inhibit myelination directly, interfere with the immune system’s T cells and also inhibit the transport of fatty acids to the myelin producing cells by interfering with IGF-1 function. Low IGF-1 function can lead to fluctuant inflammation of the myelin sheath by “herpes” activation, poor nutritional delivery of necessary fatty acids and amino acids and in severe cases growth delay. Therefore, it is extremely important to quantify the Metallothionein levels in most patients to determine if further heavy metal testing is necessary. If Metallothionein levels are lower than expected, the use of Metallothionein Promoters (MT promoters) may be utilized. In patients who have difficulty transporting heavy metals, chelation or claforation may be required.

## 2 Reduce the viral load to decrease myelin inflammation

Many physicians falsely believe that it is impossible to “kill” the herpes virus because we do not have a medication that “kills” herpes directly. This statement is short-sighted because the immune system is perfectly capable of destroying a herpes family virus. It is only essential to provide exposure of the virus to the immune system. Immune exposure is accomplished by anti-viral medications that arrest the viral division while it is outside the nerve body. This allows the immune system to have adequate time to kill the exposed virus and gradually reduce the amount of viral load in the nervous system.





### 3. Reduce fungal/bacterial/ immune hyperstimulation

It is well documented that many types of opportunistic infections can be active in the patient with Autistic Spectrum and Sensory Integration Disorders. These “opportunists” can be represented by fungal, bacterial or viral agents. Common “opportunists” include Candida, Mycoplasma, Clostridium, E. coli, measles, human papilloma virus and many others. It is essential for your physician to quantify these agents if possible and reduce the amount of immune stimulation caused by activation or overgrowth. This helps to create the “ideal” environment necessary to recover the sensory nerve deficit.



### 4. Maximize the hormonal and nutritional status

Nerves, in general, are very difficult to repair or develop. Nerves typically require the “healing” hormones (thyroid, cortisol, insulin and IGF-1) to have levels that approach the middle of the normal range for that patient’s age. These hormone levels will generally be evaluated by blood testing and adjusted in necessary.

## **Is this a new experimental treatment?**

The treatment protocol utilized by NSCA is not new or experimental. NSCA has been utilizing this therapeutic protocol for over 5 years and have treated over six thousand adults and older children with sensory dysfunction, vestibular deficits and/or cognitive and emotional syndromes. The current NSCA protocols are the result of extensive clinical research experience into diagnostic methods and treatment outcomes on patients with a single sensory deficit (i.e. vestibular dysfunction).

## **Frequently Asked Questions**

### **How long until my symptoms improve?**

Many symptoms can improve as early as 2-3 months, however, resolution of secondary symptoms may take up to 3-24 months to improve. There are 3 main phases of treatment in these patients. First, decrease the viral load will take approximately 6 months. Please remember that the inner ear is dynamic and symptoms can fluctuate from day to day and fluctuation is particularly common during the first 6-8 weeks. Each patient is treated individually according to his/her problem, and improvement may vary from patient to patient.

### **How often will I be expected to follow up with re-testing?**

The doctor would like to see re-testing done every 3 months. This re-testing provides the healthcare team with specific information to customize your plan of care and accurately follow your progress. This method is unique and above all provides the most successful approach to evaluating and treating the inner ear problem.

### **Will my insurance cover the treatment?**

Insurance is a contract between you and your insurance carrier. All of our testing is approved by Medicare and most insurance carriers. Platform Posturography is not reimbursed by Medicare in the State of Texas, but is reimbursable in other states, and may be denied by other insurance carriers. It is essential for objective verification of improvement and modification of your care plan. No testing is performed in our office without prior research indicating its' necessity and benefit to your care plan.

### **What laboratory testing do you recommend?**

At some point during the treatment phase, certain laboratory testing is invariable necessary. This testing may include tests that have not been performed previously by your physician. We typically recommend blood testing to include IGF-1, Free T4, TSH, Metallothionein profile and occasionally testosterone, estrogen and/or progesterone. Additional laboratory may be necessary depending on your condition.

# **Efficacy of the NEC Clinical Model for Management of Patients with Vestibular Related Disorders: A Retrospective Study**

## **Background:**

Vertigo and balance disorders are a frequent problem. Various studies indicate that “dizziness” is among the three most common complaints encountered in the primary care setting, sharing equal time with headaches and low back pain. Over the age of 65, it becomes one of the most common causes of office visits and hospitalizations. In 1985, more than 5 million of these office visits were documented for patients over 65 years of age, by 1994, that number had risen to 11 million.

The overall prevalence and debilitating nature of balance disorders calls for a reevaluation of the methods for diagnosis and treatment of these patients. Most practitioners falsely believe that vertigo is a self-limiting disease process and clinically respond simply by medicating and reassuring the patient. For example, over 50% of patients seen in the primary care setting for complaints of “dizziness” receive no diagnosis, yet 70% receive a prescription for Meclizine. Long-term use of this medication is at best ineffective and more than likely useless. This typical treatment is ineffective because it does not address the root of the problem, and in most cases e results in patients seeking diagnosis and relief elsewhere.

In addition, most physicians overlook the long-term, secondary symptomatology that accompanies the balance-disorder patient. Patients’ symptoms are sometimes vague and these patients may appear normal at first impression. Common complaints include hearing loss, disorientation, dysequilibrium, “foggy” headedness, “anxiety”, short-term memory loss, distractability and lack of concentration. (Usually more than one out of every three dizzy patients has been treated by four or more physicians for their complaint (Internet survey, Coping with Dizziness)). Therefore, the standard reflex therapy of medication and reassurance for all complaints of dizziness must be reevaluated and modified.

## ***Purpose:***

The purpose of this study was to investigate the efficacy of the NEC clinical protocol using a multi-discipline approach for the management of persons suffering from vestibular related disorders.

## ***Study Design:***

The project was a retrospective investigation using a pre-test/ post-test study design with repeated-measures ANOVA statistics.

## ***Methods:***

### □ ***Study Participants:***

ONE HUNDRED FIFTY-SIX PATIENT MEDICAL RECORDS WERE RANDOMLY SAMPLED FOR THIS INVESTIGATION USING INCLUSION CRITERIA. PATIENT RECORDS WERE FOR INDIVIDUALS TREATED BY THE NEC REGIONAL BALANCE CENTER OVER A 30-MONTH PERIOD FROM DECEMBER 1, 1997 TO JUNE 1, 2000. PATIENTS HAD TO HAVE BEEN TREATED BY THE CLINIC FOR AT LEAST SIX WEEKS, AND RECEIVED AT LEAST TWO DIAGNOSTIC TESTING SESSIONS.

### □ ***Outcome Variables:***

Two of the clinic's standard diagnostic testing protocols were used as outcome measures for this investigation. The Vestibular Ocular Reflex (VOR) was tested using the VORTEQ® or Vestibular Autorotation Test (VAT®) computerized systems. Both systems utilized the same protocol that used eye/head coherence measures at frequencies from 1Hz up to 5-6Hz in both the horizontal and vertical planes. Gain and phase scores for each plane were used as outcome variables.

The second diagnostic testing protocol utilized the NeuroCom EquiTest® Computerized Balance Testing system that tested the vestibular spinal reflexes (VSR) during altered sensory conditions. Patients were tested while quietly standing on a force platform under six sensory conditions altering either the visual or somatosensory inputs. Postural sway values were used as outcome measurements for this test protocol.

### □ ***Data Analysis:***

Selected VOR test variables were the Gain ( $Gn_h$  &  $Gn_v$ ) and Phase ( $Pz_h$  &  $Pz_v$ ) scores at 1Hz and 3Hz. In addition, posturography test variables included the Composite balance scores (COMP) and Center of Gravity Grid-Scores (COG). All variables were set up with two scores representing results from the initial testing session compared to the follow-up test sessions. A one-way ANOVA statistical analysis was used to compare pre- and post test scores. Alpha level was set at 0.05.

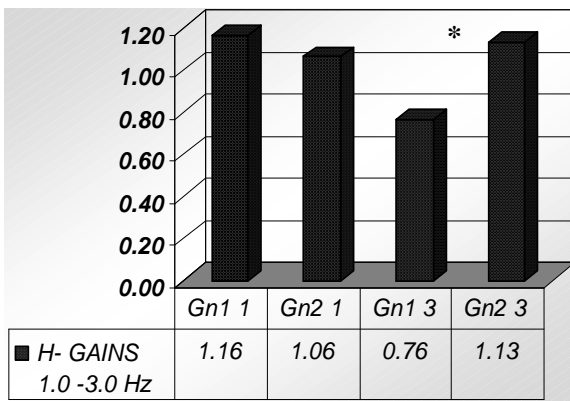
## ***Results:***

The average age for all patient charts reviewed was 45.28 (+/- 34. 5) years of age. Of the 156 total charts under review, 21% were males (33 Men and 123 women). A total of 57% had a referral diagnosis of "vertigo" and 34% were referred with a general diagnosis of "imbalance". All patients were treated with vestibular rehabilitation in addition to medical treatments to stabilize symptoms. The average length of care for all patents was 20. 86 weeks (+/- 10.12).

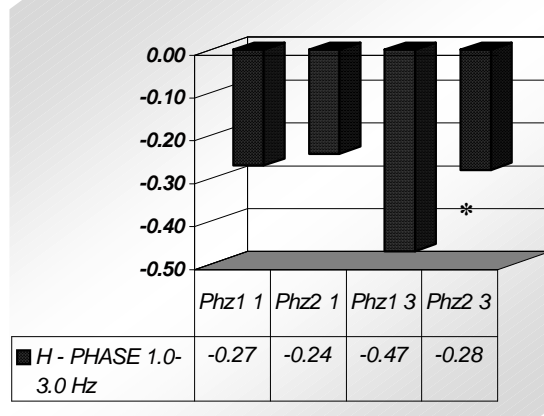
On average, mean VOR gain scores improved by 7% for frequencies at 1Hz however, most of the improvements were for gain scores at 3Hz in both the vertical and horizontal planes. (25%,  $p = 0.049$  and 49%,  $p=0.028$  respectively). Both of these improvements were statistically significant at the .05 level. Mean phase scores demonstrated significant improvements with 11% for 1Hz, 39% for 3Hz in the horizontal planes and 7% and 16% for vertical planes. Once again, values at 3Hz were found to be statistically significant ( $p= 0.047$  and  $p=0.035$  respectively). (Figures 1 & 2)

Posturography scores were found to exhibit the most change out of all variables of interest with composite balance scores improving by 28% and center of gravity scores improving by 57% overall (Figure 3). These values were statistically significant also at the 0.05 level ( $p = 0.0096$  and  $p < 0.001$  respectively).

**A.**

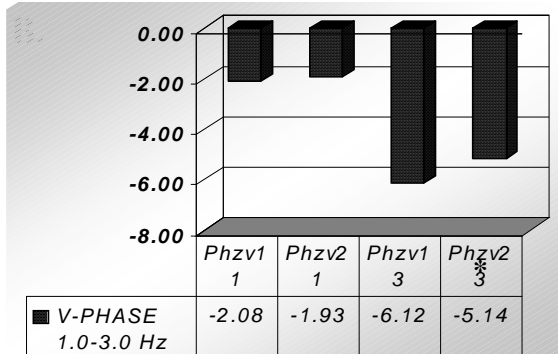
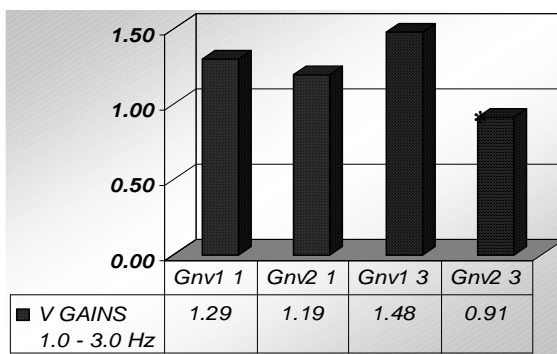


**B.**



\*  $p < 0.05$

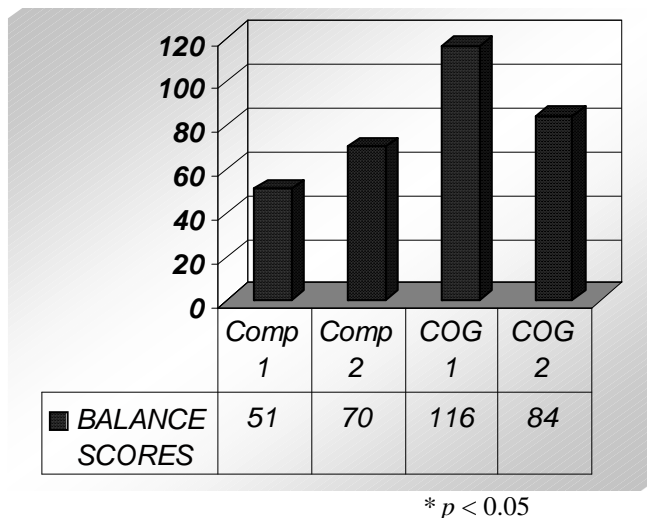
**Figure 1: Pre and Post test mean Horizontal Gain and Phase Scores for patients treated with the NEC clinical model of care for persons with vestibular disorders. A- Gains at 1.0Hz improved by 7% indicating increased coordination between eye and head amplitude in movements while the 25% improvement at 3.0z was found significant. B- Mean Phase values demonstrated an 11% improvement at 1.0Hz while improvements were 39% for 3.0Hz. These phase scores indicated decreased timing between eye and head movements. Scores at 3Hz were found to be significant.**



\*  $p < 0.05$



**Figure 2: Pre and Post test mean Vertical Gain and Phase Scores for patients treated with the NEC clinical model of care for persons with vestibular disorders. A- Gains at 1.0Hz improved by 7% while the 49% improvement at 3.0z was found significant. B- Mean Phase values demonstrated an 7% improvement at 1.0Hz while improvements were 16% for 3.0Hz. Scores at 3Hz were found to be significant.**



**Figure 3: Pre and Post-test mean Composite Balance (COMP) and Center of Gravity Grid (COG) Scores for patients treated with the NEC clinical model of care for persons with vestibular disorders. COMP scores increased overall by 28% indicated improve sensory integration under altered visual and somatosensory conditions. There was a significant 57% improvement in COG scores indicating a more centered and less scattered alignment during the balance testing.**

### **Conclusions:**

Study results indicated that a significant number of patients responded to NEC’s model of clinical care in a favorable way. The VOR and postural sway measures all indicated a significant improvement, which was apparent by diagnostic test results. VOR Gains indicated increased coordination between eye and head amplitudes during movements while phase scores demonstrated improved timing between eye and head movements. These improvements were at frequency levels typical for daily functional activities, i.e. walking (2.0-4.0Hz). Composite balance scores indicated improved sensory integration for balance under altered visual and somatosensory conditions. There was also improvement in COG mean scores indicating a more centered and less scattered alignment of the body during the balance testing. Results indicate that current clinical protocols are making a significant impact on visual stabilization at frequencies mainly around 3.Hz with also significant improvements patient sensory integration for functional balance.

## Recent Articles of Interest on Dizziness and Imbalance

Laryngoscope. 2003 Sep;113(9): 1431-8

### **Herpes simplex virus and Meniere's disease.**

**Vrabec JT.**

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**OBJECTIVE/HYPOTHESIS:** This study was designed to investigate the hypothesis that Meniere's disease is associated with herpes simplex virus (HSV) reactivation in the vestibular ganglion. **STUDY DESIGN:** Case control study. **METHODS:** Vestibular ganglia were obtained from archival surgical pathology specimens from patients undergoing vestibular neurectomy for vertigo caused by Meniere's disease. All patients met criteria for classification as definite Meniere's disease according to American Academy of Otolaryngology/Head and Neck Surgery (AAO-HNS) criteria. Control specimens were obtained from willed body donors. Sections from each ganglion were studied for prevalence of viral DNA using a nested polymerase chain reaction designed to amplify the HSV DNA polymerase gene. Quantitative analysis determined the number of viral copies per standard unit of ganglionic DNA. **RESULTS:** HSV DNA was more prevalent in paraffin embedded ganglia from patients with Meniere's disease (100%) than in fresh-frozen control ganglia (81%) ( $P = .02$ ). Fixation and paraffin embedding substantially reduced recovery of HSV virus in selected control specimens. Quantitative analysis found no correlation between viral copy number in control ganglia processed frozen versus formalin fixed and paraffin embedded. **CONCLUSIONS:** HSV is more commonly isolated from vestibular ganglia of patients with Meniere's disease than the general population. The routine histologic preparation of formalin fixation and paraffin embedding significantly altered the quantity of virus detected though not in a predictable manner. The study provides supportive evidence for a viral etiology in Meniere's disease.

ORL J Otorhinolaryngol Relat Spec. 2003 May-June;65(3): 162-8

### **Detection of viral DNA in the endolymphatic sac in Meniere's disease by in situ hybridization.**

**Yazawa Y, Suzuki M, Hanamitsu M, Kimura H, Tooyama I.**

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The main purpose of this study is to search for a viral etiology in Meniere's disease by examining the presence or absence of herpes family virus DNA in the endolymphatic sac (ES) using the in situ hybridization method. This was a prospective study with the ES from 10 patients with Meniere's disease and from 7 control cases without any pre-mortem ear diseases except a case of acoustic tumor. These 10 patients underwent the ES surgery. The presence of herpes family virus DNA, such as herpes simplex virus types 1 and 2 (HSV1&2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and human cytomegalovirus (CMV), was examined using the in situ hybridization method. Serum antibody titers against these viruses just before the ES surgery were studied in these patients. Of the 10 specimens from the patients with Meniere's disease, 7 were positive for VZV, 4 for EBV, 1 for CMV and none for HSV1&2, although the serum antibody titers against these viruses did not show any significant elevation in these patients just before the ES surgery. This result suggests that the viral DNA in the ES is inactive and is present in a latent form. From the statistical analysis, it can be postulated that VZV infection in early childhood may reach the ES and play a role in the pathogenesis of Meniere's disease ( $p = 0.0235$ ). The double infection with both VZV and EBV tended to be another candidate for the pathogenesis of Meniere's disease ( $p = 0.0557$ ). Copyright 2003 S. Karger AG, Basel

- Noise Health 2001;4(13): 71-80

## **Health profiles for patients with Meniere's disease.**

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The Nottingham Health Profile (NHP) has been used to investigate the health profiles for many medical conditions, such as herpes zoster infection, migraine, cancer and epilepsy. However, so far, it has not been used to investigate the health profile for patients suffering from Meniere's disease, but only for patients with dizziness, severe hearing loss and tinnitus. Each of these three symptoms have shown to have a significant impact on the quality of life. In the present study, 116 consecutive patients with Meniere's disease, diagnosed according to the AAO-HNS guidelines, visiting at the department of Audiology were included in the study. The NHP was used to measure the health related quality of life and includes the following subscales: "Sleep", "Energy", "Emotional reaction", "Pain", "Physical mobility", "Social isolation" and items concerning daily activity. The Tinnitus Severity Questionnaire (TSQ) was used to measure symptoms specific to tinnitus. The results showed that the perceived severity of tinnitus in patients with Meniere's disease had a significant negative influence on their health related quality of life. The patients with Meniere's disease suffered from more sleep disturbances and social isolation than patients referred to our clinic due to tinnitus. The quality of life was, on the whole, worse for patients of working age compared to retired pensioners. Emotional disturbances could explain 40.3 % of the variance of the tinnitus severity in patients with Meniere's disease. This can be compared with 20.6% in patients with tinnitus. This underscores the importance of providing psychological and psychiatric interventions and support to patients with Meniere's disease.

Am J Otol 1997 Jul;18(4): 475-83

## **Vestibular nerve pathology in cases of intractable vertigo: an electronmicroscopic study.**

**Pulec JL, Patterson MJ.**

Pulec Ear Clinic, Los Angeles, CA 90017, USA.

**OBJECTIVE:** This study aimed to determine the absence or presence and the nature of pathology of the vestibular nerve in case of intractable vertigo. **STUDY DESIGN:** This was a prospective study. **SETTING:** The study was performed at a private practice tertiary referral center. **PATIENTS:** There-were 42 patients with intractable vertigo in the study. **INTERVENTIONS:** All patients received thorough diagnostic examinations and surgical excision of the vestibular nerves. **MAIN OUTCOME MEASURES:** Segments of the superior and inferior vestibular nerves were surgically removed, preserved in glutaraldehyde, examined by electronmicroscopy, and the findings were correlated with the clinical diagnosis. **RESULTS:** A variety of different types of pathologic lesions were identified, including axon and supporting cell degeneration, herpes zoster virus, other viruses, results of bacterial infection, and regrowth of nerve after surgical resection. **CONCLUSION:** The vestibular nerves were found to be histologically normal in lesions primarily involving the end organ such as most early Meniere's disease cases, benign paroxysmal postural vertigo (BPPV), and mild labyrinthine concussion. Vestibular nerve degeneration was seen with advanced Meniere's disease, severe labyrinthine concussion, and with vascular loops in the internal auditory canal. Herpes zoster involves Scarpa ganglion in herpes zoster oticus. Viruses were found in the nuclei of vestibular nerve cells in a patient with delayed hydrops. Regrowth of the vestibular nerve after surgical resection was confirmed in three cases.

Arch Otolaryngol Head Neck Surg 1997 Jan;123(1):53-6

## **Herpes simplex virus antibodies in the perilymph of patients with Meniere disease.**

**Arnold W, Niedermeyer HP.**

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**OBJECTIVE:** To evaluate the presence of IgG antibodies directed to herpes simplex virus (HSV) in the perilymph of patients with Meniere disease. **DESIGN:** Antibodies to HSV, Epstein-Barr virus, cytomegalovirus, and measles virus were analyzed in serum and perilymph samples by enzyme-linked immunosorbent assay. Total IgG and albumin in serum and perilymph samples were measured by nephelometer analysis. The relation of specific antiviral IgG in the perilymph vs the serum was expressed as an index. **PATIENTS:** Perilymph and serum samples from 7 patients with long-standing, disabling Meniere disease were collected during therapeutic vestibulotomy. Perilymph and serum samples from 7 patients with otosclerosis and 2 recipients of cochlear implants were used as controls. **RESULTS:** Compared with the corresponding serum sample, the perilymph from the patients with Meniere disease disclosed a higher level of specific anti-HSV IgG. An elevated level of specific anti-measles virus IgG in the perilymph was detected in patients with otosclerosis. Patients of all groups showed no variation of specific anti-Epstein Barr virus IgG and anti-cytomegalovirus IgG in the serum or in the perilymph. **CONCLUSIONS:** Our results show the presence of HSV IgG in the perilymph of patients with Meniere disease and support the hypothesis that HSV may play an important role in the etiopathogenesis of Meniere disease.

Eur Arch Otorhinolaryngol, 1996;253 (4-5); 264-7

### **Detection of viral antigen in the endolymphatic sac.**

**Kumagami H.**

Department of Otolaryngology, School of Medicine, Nagasaki University, Japan.

A study was devised to determine whether or not any immune defense mechanism is present when a virus invades the human endolymphatic sac (ES). The ES was removed from 14 fresh autopsy cases having no known pre-mortem diseases in the middle and inner ears. Specimens were then examined for viral antigens including herpes simplex (HSV) type 1 and 2, mumps and cytomegalovirus using immunohistochemical methods. DNA examination by in situ hybridization was also performed for HSV. HSV antigen and DNA were observed in 9 of the 14 cases studied. These findings suggest that the virus invades the ES but is impeded by an immune defense mechanism under normal conditions. Since disease may alter host defenses, further studies are warranted to study the relationship between HSV and patients with Meniere's disease.

Arch Otolaryngol Head Neck Surg, 1995 Aug; 121(8):861-4

### **Patients with Meniere's disease possess IgE reacting with herpes family viruses.**

**Calenoff E, Zhao JC, Derlacki EL, Harrison WH, Selmeczi K, Dutra JC, Olson IR, Hanson DG.**

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**OBJECTIVE:** To determine if patients with Meniere's disease possess serum IgE specific for herpes simplex virus (HSV) type 1, HSV type 2, Epstein-Barr virus, and/or cytomegalovirus. **DESIGN:** A modified radioallergosorbent test method was employed wherein each serum sample was processed with recombinant protein A to remove competing non-IgE antibodies, and HSV-1, HSV-2, cytomegalovirus, and Epstein-Barr viral proteins were used as potential antigens. **PATIENTS:** Ten patients with long-standing active Meniere's disease were tested. Ten age- and gender-matched patients with allergic rhinitis but without Meniere's disease served as control subjects. **RESULTS:** IgE specific for HSV-1, HSV-2, Epstein-Barr virus, and/or cytomegalovirus was found in the serum sample of nine of 10 patients with Meniere's disease but only in four of 10 control serum samples. Of the positive subjects tested, seven patients with Meniere's disease were positive for IgE for at least three viruses compared with only two control subjects. **CONCLUSIONS:** (1) Most patients with Meniere's disease possess virus-specific IgE in their serum samples; (2) four viruses of the herpes family are capable of inducing such IgE-mediated sensitization; and

(3) latent virus-specific, IgE-mediated inflammation may be an important factor in the initiation and/or sustenance of Meniere's disease.

Am J Otol, 1994 Sep;15(9):639-43

### **Detection of viral DNA in endolymphatic sac tissue from Meniere's disease patients.**

**Welling DB, Daniels RL, Brainard J, Western LM, Prior TW.**

Department of Otolaryngology, Ohio State University, College of Medicine, Columbus 43210, USA.

Neurotropic viruses have been postulated to play a role in the development of Meniere's disease (MD). The purpose of this study was to evaluate the endolymphatic sacs of patients undergoing surgery for MD in a single-blind study for evidence of herpes simplex virus (HSV), varicella zoster (VZ), or cytomegalovirus (CMV) DNA. Polymerase chain reaction (PCR) was used as the method of detection because of its sensitivity, specificity, and applicability to fresh, as well as fixed tissues. Twenty-two patients with MD and 11 control patients with vestibular schwannomas had a portion of the endolymphatic sac removed at the time of surgery. The specimens were then evaluated for herpes simplex type 1, varicella zoster, and cytomegalovirus DNA. Herpes simplex virus DNA was detected in 2 of the 22 extracts from the endolymphatic sacs obtained from patients with MD. There was no evidence of a positive signal obtained with any of the other viral DNA probes when PCR was performed on the control tissue extracts or the other MD tissue extracts. These results do not demonstrate a significant difference and do not statistically support the postulate that ongoing viral infection in the endolymphatic sac is a frequent factor in the development of Meniere's disease.

Acta Otolaryngol Suppl, 1993;503:85-9

### **Latent herpes simplex virus type 1 in human vestibular ganglia.**

**Furuta Y, Takasu T, Fukuda S, Inuyama Y, Sato KC, Nagashima K.**

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Viral infection has been considered to be a possible pathogenesis of vestibular neuronitis, and reactivation of the herpes simplex virus (HSV) is one of the most likely causes. However, it remains unknown whether the human vestibular ganglia contain latent HSV. We examined 26 vestibular ganglia from autopsied adults in search of HSV type 1 (HSV-1). To detect HSV-1, we used polymerase chain reaction (PCR), in situ hybridization and immunohistochemical staining. HSV DNA was detected in 6 of 10 vestibular ganglia using the PCR method. However, the latency-associated transcript (LAT) of HSV-1 was negative in all of the 16 vestibular ganglia examined. No HSV antigen was detected in any of the ganglia. These results indicate that HSV-1 is latently infected in the human vestibular ganglia, and that LAT is transcribed weakly or not at all.

Acta Otolaryngol Suppl. 1993;503:74-8

### **Serum viral antibody titer in vestibular neuronitis.**

**Shimizu T, Sekitani T, Hirata T, Hara H.**

Department of Otolaryngology, Yamaguchi University School of Medicine, Ube, Japan.

Fifty-seven cases of vestibular neuronitis were evaluated for viral infection by means of serum antibody titer. The viruses tested were herpes simplex virus, varicella-zoster virus, cytomegalovirus, EB virus, adenovirus, influenza virus A, influenza virus B, parainfluenza virus 3, mumps virus, rubella virus and

measles virus. Paired sera were examined in 49 cases among 57 cases, 26 cases showed significant change (four-fold or greater change) in viral antibody titer. Only one case (53-year old female) showed high HSV 1 IgM antibody level by ELISA method, so the vestibular neuronitis in this case was assumed to have a close relation to viral infection.

Biomarkers. 2004 Jul-Oct;9(4-5):331-40.

### **Enzyme-immunoassay for the determination of metallothionein in human urine: application to environmental monitoring.**

**Swierczek S, Abuknesha RA, Chivers I, Baranovska I, Cunningham P, Price RG.**

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The objectives of this study were to develop an enzyme immunoassay for metallothioneins in human urine using a polyclonal antiserum and to demonstrate a possible relationship between the level of this biomarker and heavy metal exposure. The antiserum was raised in sheep against horse metallothionein conjugated to carboxylated bovine serum albumin. The antibody was used to construct a two-step competitive ELISA procedure. Human urine was treated with activated charcoal powder to remove traces of metallothioneins and known amounts of pure metallothioneins were added to provide standards for a standard curve. Metallothionein levels were measured in two groups of children living in areas of mild and high environmental pollution due mainly to heavy metals. A comparison was made between the biomarker levels and the levels of cadmium and lead in urine samples in the two groups. A group of children from a non-polluted area acted as controls. The results show that the detected levels of metallothioneins appear to correspond to levels of the two heavy metals studied and that there was an apparent relationship to the environmental exposure. Thus according to results of this study the increase in the metallothionein excretion seems to provide an indication of previous of exposure to metals. The ELISA procedure is sensitive and robust and can be used to screen large numbers of samples and is more rapid than the physical procedures currently used for analysis of these proteins. The assay can therefore be used as an additional tool for screening at-risk populations where either environmental or occupational exposure to divalent heavy metals is suspected.

### **Activation of catechol-O-methyltransferase in astrocytes stimulates homocysteine synthesis and export to neurons.**

**Huang G, Dragan M, Freeman D, Wilson JX.**

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Elevation of the total homocysteine (tHcy) concentration in plasma has been implicated in neurodegeneration in patients with stroke, dementia, Alzheimer disease, and Parkinson disease. Because the mechanisms controlling brain tHcy are unknown, the present study investigated its synthesis and transport in primary rat brain cell cultures. We found that the catechol-O-methyltransferase (COMT) substrate 3,4-dihydroxybenzoic acid (DHB) increased export of tHcy in astrocytes, but not in neurons. The export mechanism was selective for tHcy over cyst(e)ine, total glutathione (tGSH) or cysteinylglycine (Cys-Gly). tHcy export from astrocytes was also induced by the COMT substrates levodopa (L-DOPA), dopamine and quercetin, and it was blocked by the COMT inhibitors tropolone and entacapone. This export was associated with increased synthesis of tHcy because both intracellular and extracellular tHcy concentrations rose during COMT activation. Incubation in cyst(e)ine-deficient medium inhibited the tHcy export response to COMT activation. Exogenous tHcy (100  $\mu$ M) was accumulated into neurons, but not into astrocytes. We conclude that activation of COMT causes sustained synthesis of Hcy in astrocytes and transport of this amino acid to neurons.(c) 2005 Wiley-Liss, Inc.

## **Lead poisoning: a summary of treatment and prevention.**

**Cohen SM.**

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Lead poisoning affects an estimated 890,000 young children in the United States annually (American Academy of Pediatrics [AAP], 1998). Extremely high levels in the child can cause mental retardation, coma, seizures, and death. Chronic low level exposure is more commonly seen with multiple effects, including learning disabilities, impaired growth, and hearing loss. Lead poisoning prevention efforts have significantly reduced the number of children affected by this serious health hazard. Health care providers need to continue their vigilant efforts to educate families living in older homes about the risks, screening, and treatment.

Neurotoxicol Teratol, 2003 Jan-Feb;25 (1): 69-76

### **Neurotoxic effects of mercury on auditory cortex networks growing on microelectrode arrays: a preliminary analysis.**

**Gopal KV.**

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Mercury is known to cause sensorineural hearing loss and impaired speech perception. However, there is still a lack of a quantitative description of mercury toxicity on central auditory structures. This is a preliminary study using the novel technique of microelectrode array (MEA) recordings to evaluate acute and chronic neurotoxic effects of mercury on auditory cortex networks (ACNs) in vitro. Morphological and electrophysiological effects of mercuric chloride (HgCl<sub>2</sub>) were studied. Neurons dissociated from auditory cortices of 14-day-old mouse embryos were grown on photoetched MEAs containing 64 transparent indium-tin oxide (ITO) electrodes. For acute electrophysiological experiments, the spontaneous spiking and bursting activity from ACNs were compared before and after application of HgCl<sub>2</sub>. For chronic electrophysiological experiments, auditory cortex cultures were treated with various concentrations of HgCl<sub>2</sub> from the day of seeding, and were tested 4 weeks later for the presence of spontaneous activity. Morphological analysis was conducted on 8-day-old ACNs treated with HgCl<sub>2</sub> for 3 days. Results of acute experiments indicated that <75 nM of HgCl<sub>2</sub> had an excitatory effect of variable magnitude on the spontaneous activity of ACNs; however, concentrations above 100 nM completely and irreversibly inhibited spike and burst activity. Chronic exposure of ACNs to 10 nM HgCl<sub>2</sub> completely blocked the spontaneous activity. Morphological analysis indicated that 10 nM HgCl<sub>2</sub> caused neuronal cell death in 3 days. It is concluded that HgCl<sub>2</sub> has a more toxic effect on auditory networks when exposed chronically, and the levels of mercury showing toxic effects on ACNs are within the dose range shown to cause neurologic symptoms in humans.

Auris Nasus larynx. 2003 Feb;30 Suppl:S25-8

### **Zinc deficiency and tinnitus.**

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**OBJECTIVE:** To determine if there is a correlation between serum zinc levels and audiometric performance in tinnitus patients. **METHODS:** Seventy-three patients participated in this study. Patient's age was restricted to 20-59 years. All patients were examined at the otolaryngology outpatient clinic of the St. Marianna University Toyoko Hospital. The control group consisted of 38 age- and sex-matched healthy volunteers. A blood sample was taken to measure serum zinc levels. Hypozincemia was set at a level of the mean minus one S.D. in the control group. An average hearing sensitivity was calculated as the mean value of hearing thresholds at five frequencies: 250, 500, 1000, 2000, and 4000 Hz. Normal hearing was indicated when the hearing threshold at each of these frequencies was within 20 dB of normal thresholds. **RESULTS:** There was no significant difference in serum zinc levels between patients with tinnitus and

controls. However, patients with tinnitus who had normal hearing had significantly lower serum zinc levels compared to controls. In contrast, no significant difference in serum zinc levels was found between patients with tinnitus who had hearing loss, and controls. A significant correlation between average hearing sensitivity and serum zinc level was observed. **CONCLUSIONS:** These findings suggest that zinc is involved in the generation of tinnitus, especially in patients whose hearing is relatively normal.

Biol Trace Elem Res, 2002 Aug;88(2):153-63

### **Effect of zinc ion on cadmium-induced auditory changes.**

**Agirdir BV, Bilgen I, Dinc O, Ozcaglar HU, Fisenk F, Turhan M, Oner G.**

Department of Otorhinolaryngology, Faculty of Medicine, Akdeniz University, Antalya, Turkey.

Cadmium, which has adverse effects on many physiological systems, is an important environmental pollutant. Our previous experimental study showed that cadmium also has a dose-dependent deleterious effect on the auditory system in rats. Because zinc reverses cadmium cytotoxicity in many systems, we investigated the possible preventive effect of a zinc-enriched diet given isochronally on cadmium-induced hearing loss in rats. Fifty-four male rats were divided into three equal groups. Control rats were fed normal rat food and tap water, whereas the cadmium group was subjected to 15 ppm cadmium-containing water as CdCl<sub>2</sub>. The third group received 15 ppm CdCl<sub>2</sub> and food enriched with 200 ppm zinc as ZnSO<sub>4</sub> for 30 d. On d 30, eight animals from each group were used for the measurement of kidney functions. In the remaining animals, hearing functions were measured by auditory brainstem response and distortion product otoacoustic emission. Blood cadmium increased from 1.87±1.69 to 6.08±2.62 microg/dL and elevated cadmium contents of ear ossicles and kidney cortex were associated with a decreased glomerular filtration rate in rats subjected to high cadmium. A zinc-enriched diet obviously reduced cadmium accumulation in the kidney and prevented the nephrotoxicity. Our data indicated that cadmium-induced ototoxicity seems to be partially zinc preventable and zinc addition to diet without altering cadmium content in ear ossicles may help to prevent cadmium-induced hearing loss.

J Occup Environ Med. 2002Jan;44(1):30-8

### **Neuro-ototoxicity in andean adults with chronic lead and noise exposure.**

**Counter SA, Buchanan LH.**

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Brainstem auditory evoked responses and audiological thresholds were used as biomarkers for neuro-ototoxicity in adults with chronic lead (Pb) intoxication from long-term Pb exposure in ceramic-glazing work. Venous blood samples collected from 30 adults (15 men and 15 women) indicated a mean blood Pb level of 45.1 micrograms/dL (SD, 19.5; range, 11.2 to 80.0 micrograms/dL) and in excess of the World Health Organization health-based biological limits (men, 46.2 micrograms/dL; SD, 19.6; range, 18.3 to 80.0 micrograms/dL; women, 44.0 micrograms/dL; SD, 20.1; range, 11.2 to 74.2 micrograms/dL). Mean auditory thresholds at frequencies susceptible to ototoxicity (2.0, 3.0, 4.0, 6.0, and 8.0 kHz) revealed sensory-neural hearing loss in men, which may be attributable to occupational noise exposure in combination with Pb intoxication. Bilateral brainstem auditory evoked response tests on participants with elevated blood Pb levels (mean, 47.0 micrograms/dL) showed delayed wave latencies consistent with sensory-neural hearing impairment. The results suggest that environmental noise exposure must be considered an important factor in determining sensory-neural hearing status in occupationally Pb-exposed adults.

### **Abnormal auditory brainstem responses for mice treated with mercurial**



## **compounds: involvement of excessive nitric oxide.**

**Chuu JJ, Hsu CJ, Lin-Shiau SY.**

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In this paper, we attempted to construct an animal (mouse) model for monitoring the oto-neurotoxicity of mercuric sulfide, comparing its toxicity with the well-known (organic) mercury compound methyl-mercury. Mice were treated with either mercuric sulfide (HgS, 0.1 and 1.0 g/kg per day) or methyl-mercury (MeHg, 0.2, 2.0 and 10 mg/kg per day) by gastric gavage for 7 consecutive days. Analysis of auditory brainstem response (ABR) indicated that significant elevation of the physiological hearing threshold as well as significant prolongation of interwave latency I-V was observed for MeHg -- (2.0 and 0.2 mg/kg per day) or HgS -- (1.0 g/kg per day, but not 0.1 g/kg per day) treated mice. Further, both MeHg- and HgS-treated animals demonstrated a significant prolongation of interwave latency I-V that increased with an increasing mean blood-Hg level. The oto-neurotoxicity of MeHg (2.0 mg/kg per day) persisted to at least 11 weeks subsequent to the cessation of its administration. The toxic effect of HgS, however, disappeared completely 5 weeks subsequent to the cessation of its administration. These results suggest a correlation between the Hg-elicited hearing dysfunction and the availability of mercury in brain tissue. Both inhibition of Na(+)/K(+)-ATPase activity and overproduction of nitric oxide in the brainstem are consistent with an analysis of the physiological hearing threshold and latencies of ABR waveform at all time points throughout the experimental process. Thus, it is proposed that high-dose HgS or MeHg intoxication is associated with a decrease in functional Na(+)/K(+)-ATPase activity in the brainstem of affected animals, this presumably arising via excessive nitric oxide production, and suggesting that brainstem damage may play a role in mercury-induced hearing loss.

## **Lead exposure and hearing effects in children in Katowice, Poland.**

**Osman K, Pawlas K, Schutz A, Gazdzik M, Sokal JA, Vahter M.**

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The objective of the study was to investigate the relationship between lead exposure and hearing in children in the Katowice region, an industrial area in Poland. Blood lead was determined using inductively coupled plasma mass spectrometry, with appropriate quality control. The concentrations of lead in blood (B-Pb) in 155 children, aged 4-14, ranged from 19 to 281 microg/L (0.09 to 1.4 micromol/L), with a median of 72 microg/L (0.34 micromol/L). The hearing thresholds increased significantly with increasing blood lead levels at all investigated frequencies (0.5, 1, 2, 4, 6, and 8 kHz). The relationship also remained significant for B-Pb below 100 microg/L (0.48 micromol/L; n=107). The brainstem auditory evoked potential latency of wave I was significantly increased (also after adjustment for age) in the group of children with the highest blood lead levels (B-Pb above 100 microg/L, 0.48 micromol/L; n=51), compared to the group with the lowest ones (B-Pb below 46 microg/L, 0.22 micromol/L; n=51). The audiometric results clearly indicate that auditory function in children is impaired at a blood lead concentration even below 100 microg/L (0.5 micromol/L). Copyright 1999 Academic Press.

## **Occupational lead exposure and hearing loss.**

**Forst LS, Freels S, Persky V.**

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Studies of adults, children, and laboratory animals suggest an association between lead exposure and hearing loss. A causal relationship might direct mandated medical surveillance of lead-exposed workers to include audiometric testing. A cross-sectional, computerized dataset was obtained from a private occupational health screening company to examine the relationship between blood lead level and hearing loss. Audiometry and blood lead results were available for 183 workers. A statistically significant correlation was found between blood lead level and an elevated hearing threshold at 400 Hz ( $P = 0.03$ ); no other frequencies showed such a correlation. This finding suggests either an interaction between noise exposure and lead, interaction of other exposure factors (such as cigarette smoking), or that factors other than biomechanical ones render the organ of Corti more susceptible at 4000 Hz. Further evaluation of these questions should be undertaken. Computerized databases created for worker surveillance may be a source for data useful for examining other causal connections in occupational settings.

## **Diagnostic reliability of a single IGF-I measurement in 237 adults with total anterior hypopituitarism and severe GH deficiency.**

**Aimaretti G, Corneli G, Baldelli R, Di Somma C, Gasco V, Durante C, Ausiello L, Rovere S, Grottoli S, Tamburrano G, Ghigo E.**

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**OBJECTIVE:** Within an appropriate clinical context, GH deficiency (GHD) in adults must be demonstrated biochemically by a single provocative test. Insulin-induced hypoglycaemia (ITT) and GH-releasing hormone (GHRH) + arginine (ARG) are indicated as the tests of choice, provided that appropriate cut-off limits are defined. Although IGF-I is the best marker of GH secretory status, its measurement is not considered a reliable diagnostic tool. In fact, considerable overlap between GHD and normal subjects is present, at least when patients with suspected GHD are considered independently of the existence of other anterior pituitary defects. Considering the time and cost associated with provocative testing procedures, we aimed to re-evaluate the diagnostic power of IGF-I measurement. **DESIGN:** To this goal, in a large population [ $n = 237$ , 139 men, 98 women, age range 20-80 years, body mass index (BMI) range 26.4 +/- 4.3 kg/m<sup>2</sup>] of well-nourished adults with total anterior pituitary deficit including severe GHD (as shown by a GH peak below the 1st centile limit of normal response to GHRH + ARG tests and/or ITT) we evaluated the diagnostic value of a single total IGF-I measurement. IGF-I levels in hypopituitary patients were evaluated based on age-related normative values in a large population of normal subjects (423 ns, 144 men and 279 women, age range 20-80 years, BMI range 18.2-24.9 kg/m<sup>2</sup>). **RESULTS:** Mean IGF-I levels in GHD were lower than those in normal subjects in each decade, but not the oldest one (74.4 +/- 48.9 vs. 243.9 +/- 86.7 micro g/l for 20-30 years; 81.8 +/- 46.5 vs. 217.2 +/- 56.9 micro g/l for 31-40 years; 85.8 +/- 42.1 vs. 168.5 +/- 69.9 micro g/l for 41-50 years; 82.3 +/- 39.3 vs. 164.3 +/- 60.3 micro g/l for 51-60 years; 67.5 +/- 31.8 vs. 123.9 +/- 50.0 micro g/l for 61-70 years;  $P < 0.0001$ ; 54.3 +/- 33.6 vs. 91.6 +/- 53.5 micro g/l for 71-80 years,  $P = ns$ ). Individual IGF-I levels in GHD were below the age-related 3rd and 25th centile limits in 70.6% and 97.63% of patients below 40 years and in 34.9% and 77.8% of the remaining patients up to the 8th decade, respectively. **CONCLUSIONS:** Total IGF-I levels are often normal even in patients with total anterior hypopituitarism but this does not rule out severe GHD that therefore ought to be verified by provocative testing of GH secretion. However, despite the low diagnostic sensitivity of this parameter, very low levels of total IGF-I can be considered definitive evidence of severe GHD in a remarkable percentage of total anterior hypopituitary patients who could therefore skip provocative testing of GH secretion.

## **Impact of growth hormone on central nervous activity, vigilance, and**

## **tiredness after short-term therapy in growth hormone-deficient adults.**

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Impairment of well-being and cognitive function has been reported in growth hormone-deficient adults, as well as an improvement of these parameters after GH substitution, albeit inconsistently. The effect of growth hormone on central nervous activity, vigilance and sleepiness was studied prospectively in 16 growth hormone-deficient adults (7 females, 9 males, mean age: 36.8 yrs) with multiple pituitary hormone deficiencies before and 3 months after the start of growth hormone substitution using two objective methods of measurement, pupillographic sleepiness test and a choice reaction time test. Significant differences were found for neither pupillary unrest index nor for reaction time, false or missing reactions in 12 evaluable patients (7 females, 5 males, mean age 37.8 years). Because of the known interrelationships between growth hormone, sleep and mood, the visual analogue scale for tiredness and standardized retrospective questionnaires regarding sleep and mood (Pittsburgh sleep quality index, Epworth sleepiness scale, Depression scale) were used as additional methods. After GH substitution, there was no difference in sleep efficiency and daytime sleepiness, but some of the subjective sleep parameters (sleep quality and sleep latency) improved significantly. There was a tendency for mood improvement, too. Although results must be interpreted cautiously due to the small sample size, we conclude that the improved sleep and mood parameters might be caused by other indices of general well-being in our study.

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J Endocrinol Invest. 2003 Jun;26(6):588-94.

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## **Circulating free insulin-like growth-factor-I (IGF-I) levels should also be measured to estimate the IGF-I bioactivity.**

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Free IGF-I by analogy with sex and adrenal steroids and thyroid hormones, may be the major biologically active hormonal form of IGF-I. Because of methodological difficulties in measuring the free IGF-I the measurement of total IGF-I in blood is often used to assess the activity of the endocrine GH-IGF-I axis in clinical studies. However, there is currently no reliable standard reference method for circulating total IGF-I against which individual samples can be calibrated. In addition, in many of the common methods used to measure circulating total IGF-I levels, remaining insulin-like growth factor, binding proteins (IGFBPs) or binding protein fragments after sample extraction, may still interfere and produce falsely increased or decreased circulating total IGF-I levels. This latter phenomenon occurs especially under pathologic conditions. In addition, it has also been suggested that altered post-sampling integrity of IGF-I in vitro might contribute to the reported inconsistencies in circulating total IGF-I levels in literature. Although at the moment there is also no "golden standard" for the measurement of circulating free IGF-I levels, we discuss some studies in this paper that in our opinion, have demonstrated conclusively that circulating free IGF-I levels in several conditions reflect the IGF-I bioactivity better than circulating total IGF-I levels. Therefore, when evaluating the IGF-I bioactivity in health and disease, we recommend measuring also circulating free IGF-I.

J Neurosci Res. 2003 Nov 15;74(4):512-23.

## **Systemic insulin-like growth factor-I administration prevents cognitive**

## **impairment in diabetic rats, and brain IGF regulates learning/memory in normal adult rats.**

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Diabetic patients have impaired learning/memory, brain atrophy, and two-fold increased risk of dementia. The cause of cognitive disturbances that progress to dementia is unknown. Because neurotrophic insulin-like growth factor (IGF) levels are reduced in diabetic patients and rodents, and IGF can cross the blood-central nervous system barrier (B-CNS-B), the hypothesis was tested that IGF administered systemically can prevent cognitive disturbances, independently of hyperglycemia and a generalized catabolic state. Latency to escape to a hidden platform in the Morris Water Maze is used widely to test spatial memory, a hippocampus-dependent task. Adult rats were rendered diabetic with streptozotocin and implanted 4 weeks later with subcutaneous pumps that released either vehicle (D + Veh) or 20 microg/day IGF-I (D + IGF). Latency to escape to the hidden platform was prolonged in (D + Veh) versus non-diabetic rats ( $P < 0.003$ ) 10.5 weeks after the onset of diabetes. Such prolongation was prevented in (D + IGF) versus (D + Veh) rats ( $P < 0.03$ ). The data show that IGF-I can act across the B-CNS-B to prevent loss of cognition-related performance in the water maze independently of ongoing hyperglycemia and reduction in brain ( $P < 0.001$ ) and whole body weight ( $P < 0.001$ ) in diabetic rats. The hypothesis that brain IGF contributes to learning/memory was tested. An anti-IGF antibody, or preimmune serum, was infused into the lateral ventricles in non-diabetic rats. Learning in a passive avoidance task was impaired significantly in the IGF antibody versus preimmune serum-treated groups on test Days 1, 2, and 3 ( $P = 0.04, 0.02$  and  $0.004$ , respectively). The data together are consistent with a model in which brain IGF is essential for learning/memory, and a loss of IGF activity due to diabetes may contribute to cognitive disturbances. Copyright 2003 Wiley-Liss, Inc.

## **Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and thimerosal.**

**Waly M, Olteanu H, Banerjee R, Choi SW, Mason JB, Parker BS, Sukumar S, Shim S, Sharma A, Benzecry JM, Power-Charnitsky VA, Deth RC.**

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Methylation events play a critical role in the ability of growth factors to promote normal development. Neurodevelopmental toxins, such as ethanol and heavy metals, interrupt growth factor signaling, raising the possibility that they might exert adverse effects on methylation. We found that insulin-like growth factor-1 (IGF-1)- and dopamine-stimulated methionine synthase (MS) activity and folate-dependent methylation of phospholipids in SH-SY5Y human neuroblastoma cells, via a PI3-kinase- and MAP-kinase-dependent mechanism. The stimulation of this pathway increased DNA methylation, while its inhibition increased methylation-sensitive gene expression. Ethanol potently interfered with IGF-1 activation of MS and blocked its effect on DNA methylation, whereas it did not inhibit the effects of dopamine. Metal ions potently affected IGF-1 and dopamine-stimulated MS activity, as well as folate-dependent phospholipid methylation: Cu(2+) promoted enzyme activity and methylation, while Cu(+), Pb(2+), Hg(2+) and Al(3+) were inhibitory. The ethylmercury-containing preservative thimerosal inhibited both IGF-1- and dopamine-stimulated methylation with an IC(50) of 1 nM and eliminated MS activity. Our findings outline a novel growth factor signaling pathway that regulates MS activity and thereby modulates methylation reactions, including DNA methylation. The potent inhibition of this pathway by ethanol, lead, mercury, aluminum and thimerosal suggests that it may be an important target of neurodevelopmental toxins. Molecular Psychiatry advance online publication, 27 January 2004; doi:10.1038/sj.mp.4001476

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## **Intracellular zinc fluctuations modulate protein tyrosine phosphatase activity in insulin/insulin-like growth factor-1 signaling.**

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Zinc is an effector of insulin/IGF-1 signaling and has insulinomimetic effects, the molecular basis of which is not understood. The present study establishes the capacity of zinc to inhibit protein tyrosine phosphatases (PTPs) as a cause for these effects and, moreover, demonstrates modulation of the insulin response by changes in intracellular zinc. The inhibition of PTPs by zinc occurs at significantly lower concentrations than previously reported. In vitro, zinc inhibits PTPs 1B and SHP-1 with IC(50) values of 17 and 93 nM, respectively. A fluorescent probe with a similar binding constant [FluoZin-3, K(D)(Zn) = 15 nM] detects corresponding concentrations of zinc within cells. Increase of cellular zinc after incubation with both zinc and the ionophore pyrithione augments protein tyrosine phosphorylation, and in particular the phosphorylation of three activating tyrosine residues of the insulin/IGF-1 receptor. Vice versa, specific chelation of cellular zinc with the membrane-permeable N,N,N',N'-tetrakis(2-pyridylmethyl)ethylenediamine suppresses insulin- and IGF-1-stimulated phosphorylation. In the context of the emerging concept that intracellular zinc is tightly regulated and fluctuates dynamically, these results suggest that a pool of cellular zinc modulates phosphorylation signaling.

Mech Ageing Dev. 2003 Apr;124(4):371-8.

## **Interrelationships among brain, endocrine and immune response in ageing and successful ageing: role of metallothionein III isoform.**

Giacconi R, Cipriano C, Muzzioli M, Gasparini N, Orlando F, Mocchegiani E.

Metallothionein-III (MT-III) a brain-specific member of metallothionein family contributes to zinc neuronal homeostasis, and zinc is an important regulator of many brain functions, including the activity of hormone realising factors by hippocampus. Among them, somatostatin is pivotal because affecting thyroid hormones turnover and consequently thymic and peripheral immune efficiency (Natural Killer, NK) cell activity. Somatostatin is in turn affected by somatomedin-C, which is also zinc-dependent. Therefore, somatomedin-C may be a marker of somatostatin status in the hippocampus. MTs sequester and release zinc in transient stress, as it may occur in young age, to protect cells by reactive oxygen species. In order to accomplish this task, MTs are induced by IL-6 for a prompt immune and anti-inflammatory response. During ageing, MTs are high with a role of sequester of zinc, but with very limited role in zinc release because stress-like condition and inflammation is persistent. Therefore, high MTs may become to protective in young age to harmful during ageing leading to low zinc ion bioavailability for many body homeostatic mechanisms, including brain function. As a consequence, an altered physiological cascade from the brain (upstream) to endocrine and immune system (downstream) may occur. The aim of this work is to study the role of MT-III in the interrelationships among brain-endocrine-immune response in ageing and successful ageing. The main results are: (1) MT-III and IL-6 gene expressions increase in the hippocampus from old mice, in comparison with young and very old mice. (2) Somatomedin-C plasma levels decrease in old mice in comparison with young and very old mice. (3) Low zinc ion bioavailability (tested by the ratio total thymulin/active thymulin) is coupled with altered thyroid hormone turnover and depressed IL-2 in old mice in comparison with young and very old mice. (4) 'In vitro' experiments display more increments on NK cells activity by adding zinc-bound active thymulin than T3 alone. In conclusion, low MT-III in the hippocampus from young and very old mice leads to good zinc ion bioavailability that it is upstream coupled with normal hippocampal function affecting downstream normal thyroid hormones

turnover and satisfactory NK cell activity, via complete saturation of zinc-bound active thymulin molecules. Therefore, a correct MTs homeostasis is pivotal for brain-endocrine-immune response in order to reach successful ageing.

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