



“Sensory Integration”
Disorders

and

“Autistic Spectrum” Disorders



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Autistic Spectrum Disorders

Sensory Integration Disorders

It has been well documented that there is now an epidemic increase in the neurological phenomenon the medical community commonly labels as “Autistic Spectrum Disorders” or “Sensory Integration Disorders”. Since the early 1970’s, there has been an explosive increase of more than 15% in the number of diagnosed cases of “Autistic Spectrum Disorders”.



This disturbing rise in prevalence also accompanies a generalized increase in the number of neurological disorders in the general population. Unfortunately, as with many neurological diseases of unknown origin, the environment of poorly coordinated care between medical professionals have left the parents and family of these patients in the state of relative confusion and frustration. Additionally, a poor understanding of these disorders in the medical community leaves the insurance coverage for these conditions completely inadequate.

What is an “Autistic Spectrum” Disorder?

Almost all people suffer from daily to weekly fluctuations in their ability to “think”, concentrate, “focus” or imprint short-term memory. However, when this fluctuation becomes severe enough to interfere with the simple cognitive and emotional milestones of development of cognition or social function, patients then begin to be labeled as having a “Autistic Spectrum Disorder”. The term “Autistic Spectrum Disorder” is generally used by physicians to encompass a variety of symptomatic disorders that involve a fluctuation in the speed of processing of information through the brain. Each named disorder is distinguished by the severity of clinical symptoms in a particular patient, thus the acronyms for syndromes including ADHD, ADD, Autism, LD, PDD, Dyslexia, Asperger’s, CAPD and static encephalopathy.

Despite the numerous named disorders in the “Autistic Spectrum”, these disorders are all related to an abnormal function of two primary areas of the brain: 1) the **Reticular Activating System (RAS)** and 2) the **Limbic System**. The **RAS** is a nebulous area of the brain that is responsible for wakefulness and processing of all information coming to the brain or being sent from the brain. In essence, it controls the speed of all cognitive and reflex function. The **Limbic System** is the emotional center of the brain and is responsible for behavior, aggression, anxiety, mood, and activity level.

What is a “Sensory Integration Disorder”?

“Sensory Integration Disorder” was a term coined by occupational and physical therapists who treated a large amount of children with “Autistic Spectrum Disorders”. Normal patients are able to coordinate the information being presented to the brain from different sensory systems of the body. When a system is inconsistent in its’ delivery of information to the brain, the brain will not integrate and coordinate the information and will defer to the more simplistic and stable system. “Sensory Integration Disorder” describes an inability to integrate or coordinate the senses of perception and balance in a concerted effort. The type of “Sensory Integration Disorder” can be defined according to the sensory system/s being perceived correctly. The problem may involve an underlying problem with integration of the touch (proprioceptive), visual and/or vestibular (inner ear) function.

What are these disorders?

Proposed Definition

“Autistic Spectrum Disorders” and “Sensory Integration Disorders” are complicated syndromes involving fluctuation in the function of the Reticular Activating System and Limbic System.

Where is the problem in these disorders?

In order to begin to define the problem with these disorder groups, it is important to realize where the problem actually exists. One commonality of both of these groups is that they almost always have significant fluctuations in their symptoms on a day-to-day basis. In general, this means that their condition has “good” days and “bad” days. This simple realization has enormous implications.

In brain abnormalities, such as stroke, symptoms do not fluctuate. The hallmark of a brain abnormality is that it stays consistent because the brain is damaged and cannot change on a daily basis. However, in the “Autistic Spectrum” and “Sensory Integration” Disorders, these patients have notable fluctuations, sometimes in the same day. This fluctuation can only be accomplished by changes in the information feeding the brain and causing a response. This simple fact may indeed show that we have been focusing our study in the wrong place. These children do not appear to have a brain disorder, they have a disorder in feeding the brain the proper information.

Where is the problem in these disorders? Common Sense

Brain Abnormalities are “static”

**Example: stroke, hemorrhage
(stay the same everyday)**

**“Autistic Spectrum / Sensory Integration” are “dynamic”
(change from day to day)**

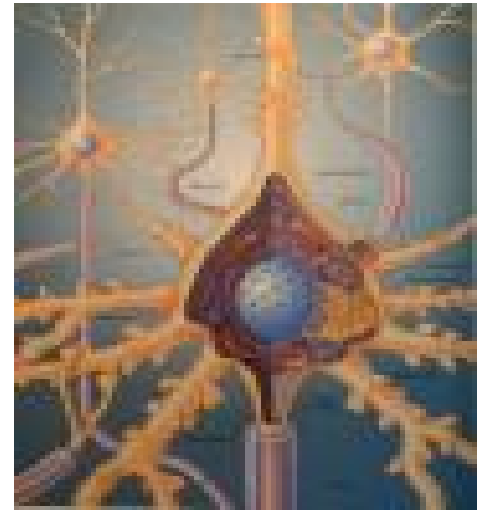
**Therefore, “Autism” and “SI” do not appear to be
primary brain problems because they rapidly fluctuate**

Normal Sensory Development

In order to understand the abnormal situation that relates to these patient groups, you must first understand normal development of the sensory systems. Normal milestones of sensory development during the first three years of life follow a methodical and predictable timeframe. The sensory nervous system is divided into subgroups according to:

1. What sense they transmit
2. How fast they carry information

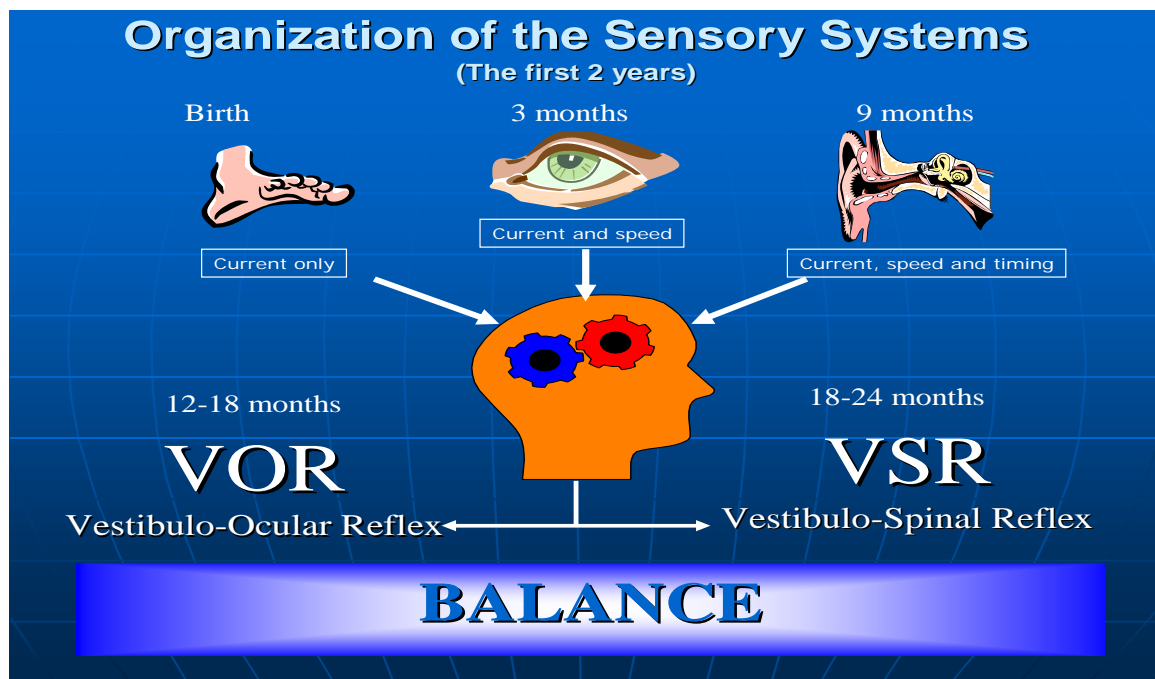
For example, touch nerves are relatively slow in speed compared to other nerves and visual nerves are ultra-fast, meaning they carry information at a very high rate. The anatomical differences between these nerves relates to the amount of myelin necessary to insulate and time the nerves speed and the size of the nerve fibers.



Birth - 3 months: Newborns initially rely on touch and feel, a "slow" system, to interact with their world. The slow speed requirement (minimal myelination) of these nerves allows them to develop sooner than other sensory nerves.

3 – 12 months: visual system begins to function. Visual nerves are "ultra-fast" and require an additional 3 months from birth to myelinate. Infants start fixing on objects and gradually develop visual tracking. This visual world is a two-dimensional world with no depth perception being present.

12 - 36 months: When the infant begins to move about, they begin feeding stable vestibular (inner ear balance) information to brain and visual system. The vestibular system is both "fast" and continuous in function and is extremely sensitive to myelination interference. Children begin to understand that there is depth to the world due to the 3-dimensional input of the vestibular system. Between the ages of 1 and 3 years, infants improve their mobility and with appropriate vestibular information begin to understand 3-dimensional visual perception and 3-dimensional body recognition. The development of the visual-vestibular system will continue to gradually refine itself until the teenage years.



How do the sensory systems work?

The primary role of the sensory systems are to interact and maintain contact with our surroundings in a safe and efficient manner. As we move through our environment, information is gathered from our vestibular (inner ear), visual (eyes) and somato-sensory (neuromuscular) systems and sent to our brainstems for integration. This information is eventually transmitted to our brain cortex for perception and processing. The Brain then coordinates a complex set of reflexes that are able to maintain or equilibrium and high speed movements without conscious thought. These reflexes include:

1. **VOR (Vestibulo-Ocular Reflex)** – stabilizes vision during high speed movement.
2. **VSR (Vestibulo-Spinal Reflex)** – maintains proper position of our extremities

How do we see the problem with the sensory systems?

Beginning in 1998, physicians began using a clinical method of combining known FDA approved diagnostic tests of sensory function to visualize the entire array of sensory functions feeding the brain at any one time. Using this diagnostic method, physicians were able to “visualize” sensory disorders and provide greatly improved therapeutic outcomes in patients with a myriad of nervous system sensory abnormalities. Testing the sensory systems typically involves extensive and time consuming diagnostics. This system has provided a unique “objective” process designed to view the function of each individual sensory system and objectively monitor the effectiveness of various therapeutic techniques.

How do Autistic Spectrum Disorders occur?

In 2002, NECA began clinical research using on Autistic Spectrum Disorders utilizing our patented diagnostic method. This research has revealed a startling consistency in abnormalities of the sensory systems and diagnostic testing in children with Autistic Spectrum Disorders. Our initial clinical research indicated that Autistic Spectrum Disorders and Sensory Integration Disorders were the same disorder. Diagnostic testing revealed consistent patterns showing that the severity of the Autistic Spectrum Disorder could be defined by the severity of the sensory misinformation being sent to the brain. Therefore, it appears quite likely that Autistic Spectrum Disorders are occur from lack of consistency or development of the patient's sensory systems.

Surprise of Initial Clinical Research 2002 (230 patients)

“Autistic Spectrum Disorders” = “Sensory Integration Disorders”

True Autism = no sensory input stability

ADHD = proprioceptive dominance (poor vision/vestibular)

ADD = 2-D visual dominance (no vestibular integration → poor 3-D vision)

LD/PDD = Occasional 3-D visual dominance (inconsistent vestibular input)

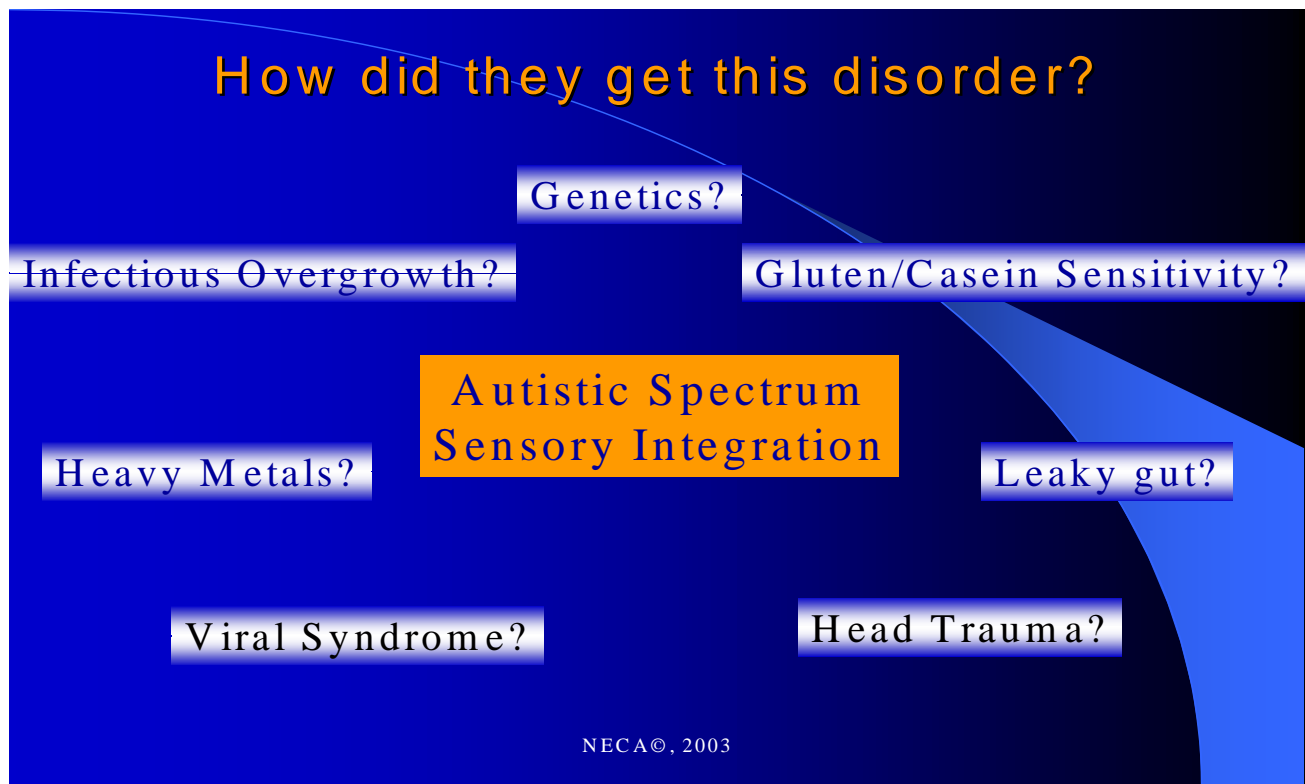
Dyslexia/CAPD = 3-D visual dominant (fluctuating vestibular)

NECA©, 2003

How did they get this disorder?

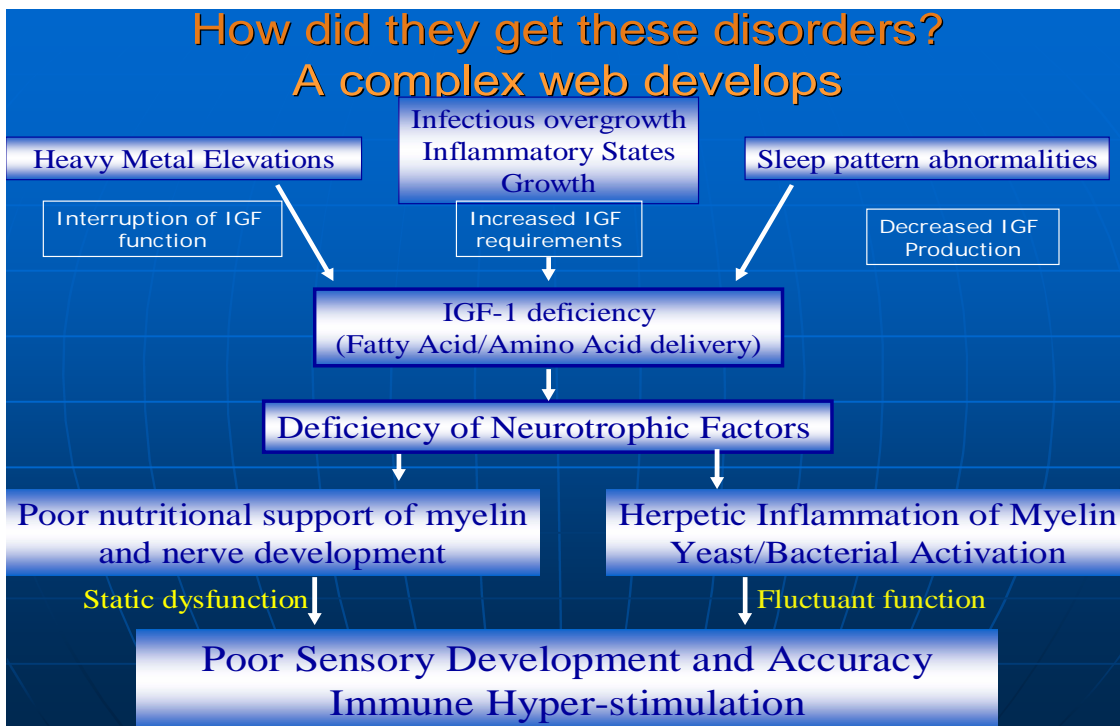
Review of the medical literature with regards to the Autistic Spectrum and Sensory Integration Disorders presents a very confusing picture to most parents and professionals. A great deal of the literature focuses on genetics, allergies, heavy metals, infectious overgrowth and enzyme abnormalities. It is important to realize that each of these abnormalities can be important and must be considered in each patient's situation. It is equally important to realize that Autistic Spectrum and Sensory Integration 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.

The NeuroSensory Center'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 a 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 and/or standard 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.

The Neuro-Sensory Centers of America’s clinical methods are based on a model that assumes that elevated heavy metal titers or viral overload initially interrupt the sensory organ development or sensory nerve myelination. Following the initial interruption in sensory development, the 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 re-activations of neurotropic (nerve infecting) viral agents cause fluctuating and frequent inflammation in the sensory organs or their nerves. This inflammation creates a fluctuating pattern of sensory mis-information and relative conflict for the brain. The variability in the sensory system function does not allow the brain to integrate the sensory systems and leads to a dynamic and confusing clinical state.



After treating several hundred patients with the “Autistic Spectrum” and “Sensory Integration” Disorders, it seems inherently clear that the maturation process of the sensory systems was stalled due to end organ damage or a clinical inability to properly myelinate the nerves of sensory function. This interference appears to have occurred due to higher

than normal heavy metal concentrations causing nutritional interference and/or chronic inflammation of the sensory nerves secondary to viral activation.

Is there a way to reverse these disorders?

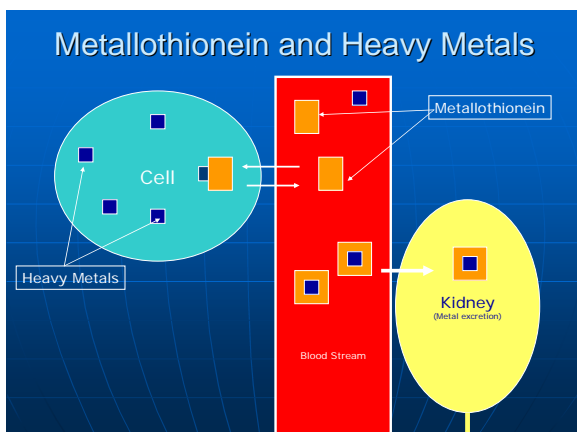
There appears to be four necessary clinical measures needed to ensure the greatest possibility of success in reversing neural disorders.

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.

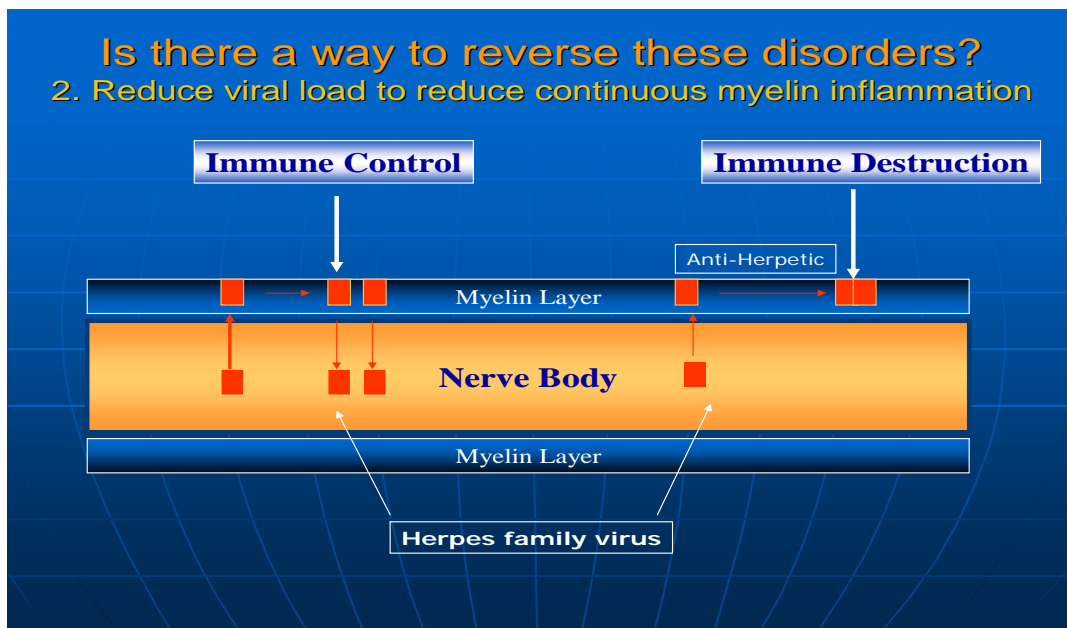


Elevated heavy metal concentrations have been shown to inhibit myelination directly, interfere with the immune system's T cells and also inhibit the transport of fatty acids to the myelin producing cells by interfering with IGF-1 function. Low IGF-1 function can lead to fluctuant inflammation of the 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 as 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

Why is sleep so important?

NSCA’s clinical research has been able to show a correlation between sleep abnormalities and nervous system abnormalities. This correlation seems to be related to an absence of Stage IV sleep, commonly known as “deep sleep”. During Stage IV sleep the body produces a group of hormones called Insulin Dependent Growth Factors (IGF I-IV), substances that are related to growth hormone. The IGF hormones are probably misnamed and should be called “Human Repair Hormones” because they are important throughout life. These factors are required for the transport of proteins, fats and cholesterol into cells.

All patients with Autistic Spectrum Disorders have difficulty entering Stage IV sleep and will typically have low normal or abnormal levels of IGF. In adults, a deficiency of these hormones causes only one symptom; fatigue. Fatigue is almost a universal complaint of all patients with nervous system abnormalities. Many times children cannot explain the feeling of fatigue. Deficiency of this hormone will be seen clinically as an increase in body fat, growth delay, poor muscle tone or weakness, and an increase in cholesterol and triglyceride levels in the blood stream.

Recent Articles of Interest

Neurotoxicology. 2005 Jan;26(1):1-8

Thimerosal Neurotoxicity is Associated with Glutathione Depletion: Protection with Glutathione Precursors.

James SJ, Slikker W 3rd, Melnyk S, New E, Pogribna M, Jernigan S.

Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital Research Institute, Little Rock, AR 72202, USA.

Thimerosal is an antiseptic containing 49.5% ethyl mercury that has been used for years as a preservative in many infant vaccines and in flu vaccines. Environmental methyl mercury has been shown to be highly neurotoxic, especially to the developing brain. Because mercury has a high affinity for thiol (sulfhydryl (SH)) groups, the thiol-containing antioxidant, glutathione (GSH), provides the major intracellular defense against mercury-induced neurotoxicity. Cultured neuroblastoma cells were found to have lower levels of GSH and increased sensitivity to thimerosal toxicity compared to glioblastoma cells that have higher basal levels of intracellular GSH. Thimerosal-induced cytotoxicity was associated with depletion of intracellular GSH in both cell lines. Pretreatment with 100µM glutathione ethyl ester or N-acetylcysteine (NAC), but not methionine, resulted in a significant increase in intracellular GSH in both cell types. Further, pretreatment of the cells with glutathione ethyl ester or NAC prevented cytotoxicity with exposure to 15µM Thimerosal. Although Thimerosal has been recently removed from most children's vaccines, it is still present in flu vaccines given to pregnant women, the elderly, and to children in developing countries. The potential protective effect of GSH or NAC against mercury toxicity warrants further research as possible adjunct therapy to individuals still receiving Thimerosal-containing vaccinations.

Biomarkers. 2204 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.

Silesian Technical University, M. strzody str.9, 44-100 Gliwice, Poland.

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 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.

Glia.2005 Mar18;

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

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

Department of Physiology and Pharmacology, University of Western Ontario, London, Ontario, Canada.

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 μ 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.

Clin Endocrinol (Oxf). 2003 Jul;59 (1): 56-61

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.

Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Turin, Italy.

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/m²] 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/m²). **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.

Horm Metab Res. 2003 Feb;35(2):114-9.

Impact of growth hormone on central nervous activity, vigilance, and tiredness after short-term therapy in growth hormone-deficient adults.

Pavel ME, Lohmann T, Hahn EG, Hoffmann M.

Division of Endocrinology, Department of Internal Medicine I, University of Erlangen-Nurnberg, Germany. marianne.pavel@med1.imed.uni-erlangen.de

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.

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

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

Janssen JA, van der Lely AJ, Lamberts SW.

Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. j.a.m.j.l.janssen@erasmusmc.nl

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.

Lupien SB, Bluhm EJ, Ishii DN.

Department of Biomedical Sciences, Colorado State University, Fort Collins, CO 80523, USA.

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.

Mol Psychiatry. 2004 Jan 27 [Epub ahead of print]

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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.

¹Department of Pharmaceutical Sciences, Northeastern University, Boston, MA 02115, USA.

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

Exp Cell Res. 2003 Dec 10;291(2):289-98.

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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.

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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.

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

Detection of viral antigen in the endolymphatic sac.

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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.

Acta Otolaryngol Suppl. 1993;503:85-9.

Latent herpes simplex virus type 1 in human vestibular ganglia.

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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.

Pediatr Nurs. 2001 Mar-Apr;27(2):125-6, 129-30.

Lead poisoning: a summary of treatment and prevention.

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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.

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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 (HgCl₂) 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 HgCl₂. For chronic electrophysiological experiments, auditory cortex cultures were treated with various concentrations of HgCl₂ 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 HgCl₂ for 3 days. Results of acute experiments indicated that <75 mM of HgCl₂ had an excitatory effect of variable magnitude on the spontaneous activity of ACNs; however, concentrations above 100 microM completely and irreversibly inhibited spike and burst activity. Chronic exposure of ACNs to 10 microM HgCl₂ completely blocked the spontaneous activity. Morphological analysis indicated that 10 microM HgCl₂ caused neuronal cell death in 3 days. It is concluded that HgCl₂ 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.

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

Effect of zinc ion on cadmium-induced auditory changes.

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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 CdCl₂. The third group received 15 ppm CdCl₂ and food enriched with 200 ppm zinc as ZnSO₄ 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. 2002 Jan;44(1):30-8.

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

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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.

Toxicology. 2001 Apr 12;162(1):11-22.

Abnormal auditory brainstem responses for mice treated with mercurial compounds: involvement of excessive nitric oxide.

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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.

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

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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.

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Occupational lead exposure and hearing loss.

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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.