Autism Rising Part 2

Metabolic, Genetic and Environmental Mysteries

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"Twenty percent of the known factors associated with autism are genetic, but most are not. It's wrong to think of genes and the environment as separate and independent factors. Genes and environmental factors interact. The net result of this interaction is metabolism." Robert Naviaux UCSD School of Medicine (43)

Researchers have been scrambling to unlock the mysteries behind the alarming rise in autism spectrum disorders (ASD). Autism causes a dismaying amount of suffering, loss of human potential as well as financial burden. ASD is increasingly recognized as a serious public health problem. According to the Centers for Disease Control and Prevention, the prevalence for ASD has risen 1200-1500% over 20 years and is now over 1%. It affects about 1 in 68 children (one in 42 boys and one in 189 girls). Is this a real phenomenon or just heightened awareness and better diagnosis? It is both. Research indicates that changes in diagnostic criteria have accounted for some but not all of the increase. In California from 1992- 2005 the criteria for inclusion changed and it is estimated that it accounted for about 25% of the increase in diagnosis.

(1)

Complex Brain Systems-Complex Brain Research

Autism is a complex disorder. A plethora of research has also discovered those with ASD have many abnormalities in the brain including …loss of cell function, signaling dysfunction, loss of purkinje cells and astrocytes, metabolism disorders, mitochondrial disorders, oxidative damage, inflammation of the brain, mast cell activation, reduction of protein synthesis, overstimulation of some areas of the brain involved in memory, alteration in the excitatory/inhibitory imbalance of glutamatergic/GABAeric system and systemic immune dysfunction all connected to the functional behavioral problems seen in autism. How are these connected with one diagnosis?

Faulty Genes and the Environment

Research suggests that a myriad of faulty genes are associated with autism however differences in gene expression and exposure to environmental factors may contribute to differing autism-related traits. (5) In fact studies of concordant twins suggest there is a stronger environmental component than previously believed.(6)(70)(71) Genetic, environmental, and immunological factors all appear to play a role in its pathogenesis. **This is an important recent shift in**

thinking about the issue as researchers are now looking at environmental influences in addition to genetic links to autism. Identifying the specific biochemical and anatomic abnormalities of ASD as well as the suspected environmental causes and triggers will help not only in treatment but also urgently guide preventative actions for this difficult and costly syndrome.

Environmental Causes or Contributors Need to be Addressed

As discussed in Autism Part 1 we are regularly exposed to a host of known neurotoxins and biologic toxins including heavy metals, pesticides, plastics, industrial chemicals, flame retardants, air pollutants, food additives and radiation. Umbilical cord samples show babies have some 200 known toxins that have been circulating in their bloodstream during fetal development. Known neurotoxins easily cross the blood brain barrier. (44,45) Endocrine disruptors are likely suspects as well considering the development and functioning of the nervous system is intimately tied to immune, reproductive and thyroid hormones during development both prenatally and postnatally. (87)(89)

What interactions do these have on the developing brain? Is it just the brain that is out of order in autism? Although there is much research to be done we know a great deal about mechanisms of toxicity for environmental exposures and how they exert their effects on cells and metabolism. In Autism Rising Part 1 these concepts were introduced. In Part 2 we will focus on the highlights of current research into genetic, biochemical changes and pathophysiology. We will then look at how researchers have connected at least some of the dots with regards to gene and environment interactions. Scientists and experts in neurotoxicology are especially concerned and are now calling for a precautionary and preventative strategies with regards to potential environmental factors.

"We need a systematic search for potentially preventable environmental causes of autism," Dr. Philip Landrigan, Director of the Children's Environmental Health Center, Mt. Sinai

Autism

Autism Spectrum Disorder (ASD) is a behaviorally defined group of neurodevelopmental disorders characterized by impairments of social interaction, communication and restricted, repetitive and stereotyped patterns of behavior, interests and activities. Individuals with autism vary widely in abilities, intelligence, and behaviors. From 30% to 60% of children with an autism spectrum disorder have an IQ measure that falls in the intellectual disability range. (3) It is generally diagnosed within the first 3 years of life during a time of critical and fragile circuit refinement.

Autism is more common in boys by a factor of 4. Some show signs of autsim in infancy while others may grow normally the first few years then suddenly become withdrawn or loose language. (58) Many individuals with ASDs have symptoms of associated medical conditions,

including seizures, sleep problems, metabolic conditions, and gastrointestinal (GI) disorders, which have significant health, developmental, social, and educational impacts. (34)

Behavioral symptoms include poor eye contact, language difficulty, inappropriate social interaction, repetitive motion or rocking, constant motion, difficulty with changes in routine,

"Work on the maternal infection risk factor using animal models indicates that aspects of brain and peripheral immune dysregulation can begin during fetal development and continue through adult- hood." (63)

Thinking Beyond Genes

Although there has been a dizzying flow of reports in the last 5 years showing hundreds of genetic alterations associated with ASD there is no one gene or set of genes found to explain autism. (54) Many cases are sporadic, with no one else in the family affected. Studies in cases where there is no family history show about 10% de novo gene mutations. (67) In addition spontaneous epigenetic changes in the DNA (methylation without DNA sequence changes) can also play a role in behavior disorders according to twin studies. (7)(70)(71) A variety of toxicants and endocrine disruptors have also been implicated alone or in combination. Endocrine disrupting chemicals may be a factor as males are 4 times more likely to be autistic suggesting estrogen/testosterone alteration. In addition adrenal, gonadal, and thyroid hormones play an important role in fetal neurodevelopment. "Any chemical that interferes with the actions of these hormones therefore has the potential to disrupt brain development."(88)

Autism Risk Factors:

Maternal Infection, Preterm Delivery, Paternal age, Air Pollution

Autism appears to be a heterogenous disorder that is influenced by multiple defective gene family interactions along with environmental factors.(62) In addition genes affected by mutations in autism overlap those mutated in schizophrenia and intellectual disability. Also autism risk is known to be elevated with maternal infection, preterm birth, paternal age and exposure to air pollution. (63)(66)(97)(98) "Progress … has not yet led to a unified understanding of ASD pathogenesis or explained its highly variable clinical expression. With an increasingly firm genetic foundation, the coming years will hopefully see equally rapid advances in elucidating the functional consequences of ASD genes and their interactions with environmental/experiential factors, supporting the development of rational interventions." (54)

Common Aspects of Impairment:

Immune System, Inflammation, Oxidative Stress

Of the hundreds of studies already done there appear to be some common aspects of biochemical changes and metabolism that link altered genes to environmental factors. A review of research trends shows a strong association between ASD and immune dysregulation and inflammation (416 articles), Oxidative stress (115 articles), mitochondrial dysfunction (145 articles) and

toxicant exposures (170 articles). (46) In addition many articles point to subgroups with imbalances in the inhibitory/excitatory and glutamate signaling, a common biologic pattern seen in ADHD and schizophrenia as well. (60) Toxic chemicals and radiation also cause biochemical changes in cells, reactive oxygen species (ROS) and inflammation that are linked to chronic disease.

"Overproduction of reactive oxygen and nitrogen species can result from exposure to environmental pollutants, such as ionizing and non-ionizing radiation, ultraviolet radiation, elevated concentrations of ozone, nitrogen oxides, sulphur dioxide, cigarette smoke, asbestos, particulate matter, pesticides, dioxins and furans, polycyclic aromatic hydrocarbons, and many other compounds present in the environment. It appears that increased oxidative/nitrosative stress is often neglected mechanism by which environmental pollutants affect human health." (49) In fact some antioxidants have been shown to have protective effects on cells exposed to ROS. (49)

Behavior Disorders Linked to Immune System Dysfunction

A particularly difficult aspect of ASD is intense reactivity, repetitive and difficult behaviors. A link between altered immune responses and ASD was first recognized nearly 40 years ago. Neurobiological research in ASD has highlighted pathways involved in neural development, synapse plasticity, structural brain abnormalities, cognition and behavior. "Several lines of evidence point to altered immune dysfunction in ASD that directly impacts some or all these neurological processes. Extensive alterations in immune function have now been described in both children and adults with ASD, including ongoing inflammation in brain specimens, elevated pro-inflammatory cytokine profiles in the CSF and blood, increased presence of brain-specific auto-antibodies and altered immune cell function. These dysfunctional immune responses are associated with increased impairments in behaviors characteristic of core features of ASD, in particular, deficits in social interactions and communication. This accumulating evidence suggests that immune processes play a key role in the pathophysiology of ASD." (17, 20, 21)

"**Our results surprisingly converge upon immune, and not neurodevelopmental genes, as the most consistently shared abnormality in genome-wide expression patterns.** A dysregulated immune response, accompanied by enhanced oxidative stress and abnormal mitochondrial metabolism seemingly represents the common molecular underpinning of these neurodevelopmental disorders." Lintas 2012(35)

"Widespread changes in the immune systems of individuals with ASD have been identified, in particular increased evidence of inflammation in the periphery and central nervous system." 48

Key Signaling Cytokines increased with Inflammation in Autism

Cytokines are proteins involved in cell signaling and are produced by a variety of cells including macrophages, B and T lymphocytes, mast cells, fibroblasts. They are important in modulating the immune system, inflammation, infection, cancer and reproduction. (22)

Groundbreaking work by Pardo has shown an inflammatory-like state in postmortem autism brains of all ages as indicated by elevated cytokines and activated microglia and astrocytes. "Our findings indicate that innate neuroimmune reactions play a pathogenic role in an undefined proportion of autistic patients."(65)

Smith looked at maternal immune stimulation in mice and found a specific cytokine IL-6 that accurately reproduces the abnormal autistic/schizophrenic like behavior in offspring by changing gene expression.(86)

Ashwood showed significant increases of a variety of plasma cytokines in ASD. **"These findings suggest that ongoing inflammatory responses may be linked to disturbances in behavior and require confirmation in larger replication studies." (18)**

Mitochondria Dysfunction and Autism

Basic science research has now linked mitochondrial abnormalities with abnormal brain development in a subgroup of autism. Mitochondria are intracellular power plants with a three layer phospholipid membrane and a nucleus containing DNA. They use oxygen to create adenosine triphosphate or ATP, the chemical energy used in all our cells. The production of cellular antioxidant glutathione is dependent on ATP. The inner folded membrane where ATP is made is called the cristae. Precise regulation of calcium signaling is necessary for proper functioning and dysregulated mitochondrial calcium has been implicated in several neurodegenerative diseases. In addition mitochondria are sensitive to free radical formation and oxidative stress which can cause damage to the membrane and DNA causing dysfunction of the mitochondria.

Vulnerable Mitochondria

Rose found that a subset of children with autism have more vulnerable mitochondria. He states "lymphoblastoid cell lines derived from children with autistic disorder have an abnormal mitochondrial reserve capacity before and after exposure to reactive oxygen species … The results of this study suggest that a significant subgroup of ASD children may have alterations in mitochondrial function, which could render them more vulnerable to a pro-oxidant microenvironment as well as intrinsic and extrinsic sources of ROS such as immune activation

and pro-oxidant environmental toxins. These findings are consistent with the notion that ASD is caused by a combination of genetic and environmental factors." (41)

Valenti has shown that mitochondrial dysfunction is a central actor in intellectual disability-related diseases such as Down syndrome, autism, Fragile X and Rett syndrome. (24) "The prevalence of developmental regression (52%), seizures (41%), motor delay (51%), gastrointestinal abnormalities (74%), female gender (39%), and elevated lactate (78%) and pyruvate (45%) was significantly higher in ASD with Mitochondrial Disorder(MD) compared with the general ASD population**….Most ASD/MD cases (79%) were not associated with genetic abnormalities, raising the possibility of secondary mitochondrial dysfunction. (25)** "Therapeutic approaches are aimed at improving intellectual disability by activating mitochondrial function and reducing oxidative stress to ameliorate the quality of life in the subjects affected." (24)

Oxidative Stress, Glutathione and Autism

Oxidative stress and glutathione (GSH) levels are another major focus of research. There is increasing evidence of oxidative stress and reactive oxygen species (ROS) formation in the pathophysiology of autism.

Reactive Oxygen Species: Darth Vader of molecules

Reactive Oxygen Species (ROS) are chemically active molecules that are normally formed in our cells due to natural processes such as infection and can help kill unwanted bacteria. Under normal conditions ROS serve as messengers in the regulation of intracellular signaling. Excess ROS is harmful and may induce irreversible damage to our cellular components and lead to cell death through mitochondrial pathways. ROS can cause damage to DNA, enzymes, fatty acids and proteins.

Glutathione: Our Personal Antioxidant

Glutathione is the major antioxidant produced in all cells in the human body as well as in plants, fungi and bacteria. It serves to protect and balance the organism from damage caused by free radicals also known as reactive oxygen species which in excess destroy cell structures. In addition it helps to preserve important antioxidants such as vitamin C and E. After its protective antioxidant reaction is complete glutathione is regenerated back to its useful state by the enzyme glutathione reductase.

Glutathione is essential in other vital biochemical functions such as energy utilization, immune system activity, detoxification and disease prevention. "Glutathione (GSH) and related enzymes are critical to cell protection from toxins, both endogenous and environmental, including a number of anti-cancer cytotoxic agents." (38) Natural glutathione production can be disrupted by toxins such as paraquat. (37)

Reactive Oxygen Species in Autism

"Markers of oxidative damage to proteins, oxidative damage to DNA reduced glutathione, chronic inflammation were found in the brain tissue of autistic individuals compared to controls." (26) **"Glutathione is involved in neuro-protection against oxidative stress and neuro-inflammation in autism by improving the anti-oxidative stress system. Decreasing the oxidative stress might be a potential treatment for autism.** " (27)

In an earlier review article McGinnis states "Brain and gut, both abnormal in autism, are particularly sensitive to oxidative injury. Higher red-cell lipid peroxides and urinary isoprostanes in autism signify greater oxidative damage to biomolecules. A preliminary study found accelerated lipofuscin deposition--consistent with oxidative injury to autistic brain in cortical areas serving language and communication. Double-blind, placebo-controlled trials of potent antioxidants--vitamin C or carnosine--significantly improved autistic behavior. Benefits from these and other nutritional interventions may be due to reduction of oxidative stress. Understanding the role of oxidative stress may help illuminate the pathophysiology of autism, its environmental and genetic influences, new treatments, and prevention." (28)

"Several lines of research support the view that both genetic and environmental factors influence the development of abnormal cortical circuitry that underlies autistic cognitive processes and behaviors" Pardo (65)

Mechanisms of Toxic Exposure in Autism

Review of Environmental Toxicants

Rossignal identified many toxicants that may act synergistically with genetic factors at critical times of development to increase ASD. These include "pesticides, phthalates, polychlorinated biphenyls (PCBs), solvents, toxic waste sites, air pollutants and heavy metals, with the strongest evidence found for air pollutants and pesticides." (73)

Toxins Create Reactive Oxygen Species:

Toxins such as tobacco, chemicals, hormone disruptors and both ionizing and non ionizing radiation in the environment stimulate reactive oxygen species. This is one mechanism of injury leading to chronic disease and cancer. (110) Natural antioxidants such as glutathione and superoxide dismutase that protect cellular processes may become overwhelmed by this toxic exposure. Antioxidant glutathione levels can drop and protection of cells is abolished leaving the cell and the organism more vulnerable to other toxic exposures we commonly encounter.

Bisphenol A causes Oxidative Stress

Bisphenol A, a known endocrine disruptor with widespread exposure, appears to be an environmental risk factor in genetically susceptible autistic children as it also causes increased oxidative stress and mitochondrial dysfunction. (8)

Neurodevelopmental Toxins Deplete Glutathione causing or contributing to Autism

Waly and Deth from Northeastern University in Boston published a sentinel paper in 2008 on the link between neurodevelopmental toxins and autism. It also explains how one or more biochemical disruptions can be involved. (30)

They looked at ethanol, arsenic, lead, mercury, aluminum and the vaccine mercury preservative thimerosal which are suspected to be etiological factors for neurodegenerative and neurodevelopmental disorders. They note "Autism is a neurodevelopmental disorder characterized by oxidative stress and impaired methylation status, including decreased activity of the folate and vitamin B12-dependent enzyme methionine synthase (MS). MS-mediated conversion of homocysteine to methionine is crucial for neurons and all mammalian cells to sustain normal methylation status, involving more than 100 different reactions. Glutathione (GSH) protects MS from oxidative inactivation by reactive oxygen species, while MS inactivation increases GSH synthesis by augmenting transsulfuration. Utilizing cultured human neural cells, we found that a 1 hour pre-incubation of cells with arsenic, lead, mercury, aluminum and thimerosal ….caused a 60–70% reduction of intracellular glutathione. Our findings suggest that heavy metals and ethanol may contribute to the occurrence of neurodevelopmental disorders such as autism via a mechanism that involves oxidative stress and inhibition of MS activity."(30)

Deth concludes "oxidative stress, initiated by environment factors in genetically vulnerable individuals, leads to impaired methylation and neurological deficits secondary to reductions in the capacity for synchronizing neural networks." (31)

Agarwal also demonstrated that arsenic, mercury and lead caused decreased glutathione and surperoxide dismutase levels along with oxidative stress.(72)

"This study confirms earlier studies that implicate toxic metal accumulation as a consequence of impaired detoxification in autism and provides insight into the etiological mechanism of autism." (76)

Mercury Targets Brain Cells

Prior to concerns about vaccinations mercury has been a well established neurotoxin. The phrase "mad as a hatter" was coined to describe toxic symptoms of millners as mercury was used in the manufacture of felt hats in the 18th and 19th century. Manifestations were tremor, ataxia, fatigue, visual field constriction. With severe poisoning the patient is in a mute semi-rigid position with primitive motion and speech.

The experience at Minamata Japan in the 1950's where over 2,000 adults and children suffered mercury poisoning over time from ingesting fish contaminated by mercury from a nearby plant is long remembered. It was the first incident that led to the discovery that a poison such as mercury could cross the blood brain barrier. Prior to that everyone thought the blood brain barrier was impermeable to toxins. Many children born to mothers who ingested mercury had delayed motor and development, ataxia, intellectual disability and convulsions. (94)

Small doses of mercury can disrupt normal neurological development both in utero and in early life. Mercury can also be toxic to the kidneys, digestive and immune system. It is on the World Health Organizations top 10 list of chemicals of major public health concern. (94)

A University of Calgary rapid speed video of neural degeneration shows the powerful effect of mercury toxicity. (84)

Despite the fact that manufacturers have removed mercury from most vaccines there is still widespread exposure to mercury. Exposure occurs largely from eating larger predator fish such as tuna and swordfish but there is also concern about mercury in amalgam fillings and pharmaceuticals(thimerasol). Elevated mercury is of special concern for pregnant women. Biomonitoring in the U.S. has shown that there are elevated levels of mercury in 6-15% of childbearing women that could pose a risk for normal neurodevelopment. (95)

Mercury from Power Plants

Mercury is also released from coal fired power plants and cement kilns. Palmer in 2006 reported in an epidemiological study noting "a significant increase in the rates of special education students and autism rates associated with increases in environmentally released mercury. On average, for each 1,000 lb of environmentally released mercury, there was a 43% increase in the rate of special education services and a 61% increase in the rate of autism." (99)

Lead body-burden was associated with ASD severity… This study helps to provide additional mechanistic support for Lead in the etiology of ASD severity" (77)

Elevated Heavy Metals Found in Hair of Autistic Children

Multiple studies have found elevated levels of heavy metals such as lead and mercury in autistic children thus implicating toxic metal accumulation as a consequence of impaired detoxification

in autism in addition to exposure. (75)(77)(78)(79)(80)(81)"data showed that the patients with autism spectrum disorder had significantly higher lead and mercury levels and lower glutathione-s-transferase activity and vitamin E concentrations compared with the controls" Alabdali 2014 (78)

Geler in 2012 used hair toxic element testing for arsenic, mercury, cadmium, lead, chromium, cobalt, nickel, aluminum, tin, uranium, and manganese. He found "Increasing hair mercury concentrations significantly correlated with increased ASD severity but…no significant correlations were observed between any other of the hair toxic metals examined and ASD severity." (77)

Lakshmi in 2011 looked at trace mineral levels that may be beneficial - copper, zinc, magnesium and selenium versus toxic elements -mercury and lead in the hair and nail samples of autistic children to evaluate whether the level of these elements could be correlated with the severity of autism. She found "The significant elevation in the concentration of copper, lead, and mercury and significant decrease in the concentration of magnesium and selenium observed in the hair and nail samples of autistic subjects could be well correlated with their degrees of severity." (78)

"The regular and long term use of microwave devices (mobile phone, microwave oven) at domestic level can have negative impact upon biological system especially on brain. It also suggests that increased reactive oxygen species (ROS) play an important role by enhancing the effect of microwave radiations which may cause neurodegenerative diseases." (119)

Wireless Communications:

Effects of EMF Radiation on Biological Systems

Wireless technologies are ubiquitous today but were developed only in the last 20 years with a steady and sharp increase in their use and exposure since then. Several decades of peer reviewed research has confirmed that microwave radiation from a variety of wireless devices such as cell phones, WiFi routers, smart meters and baby monitors have non-thermal adverse biologic effects on a cellular level. These include leakage of the blood brain barrier, genetic damage with single and double stranded DNA breaks, disruption of intracellular communication, immune system deregulation, allergic response, altered sperm function, cardiovascular effects, abnormal protein synthesis, reactive oxygen species and alteration of DNA expression. (131)(132) In addition several studies have confirmed sperm genotoxicity after exposure to wireless EMF radiation.

Epidemiological studies have demonstrated an increase in brain tumors, with long term cell phone use- over 10 years. (124) Neurobehavioral effects from EMF have been reported to include memory loss, tinnitus, headaches, hearing loss and insomnia. Electrosensitivity to

wireless devices and EMF is officially recognized as a functional impairment in Sweden and affects about 3% of the population. (117)(118)

Schoolchildren have reported electrosensitivity in school after wi fi was placed with symptoms of headache, rapid heart beat, nausea, weakness, shakiness and rashes. It did not occur when they were home. (120)

Considering the wide range of cellular effects from microwave EMF it seems plausible that WiFi communications would contribute to autistic development through de novo mutations or exacerbate symptoms due to reactive oxygen species production thus overwhelming glutathione stores.

Many scientists throughout the world have been calling for a reevaluation of the international standards for EMF as they are not protective of human health.

The current RF-EMFstandards are based solely on heat effects of the microwave radiation on tissue and not the biological effects seen in the laboratory at levels more than a hundred times lower than what is allowed and considered safe.

EMF and Reactive Oxygen Species

EMF from wireless devices has been shown to cause reactive oxygen species and enhance free radical formation in numerous studies. (101)(102)(103)(104)(105)(106)(107)(108)(109)(111)

Lui found that exposure to radiofrequency electromagnetic radiation (RF-EMR) emitted from mobile phones induced DNA damage in male germ cells. He concluded that "these findings may imply the novel possibility that RF-EMR with insufficient energy for the direct induction of DNA strand breaks may produce genotoxicity through oxidative DNA base damage in male germ cells." (103)

"We present the first experimental evidence of neuropathology due to in-utero cellular telephone radiation." (129)

Affects on Sperm: Implications for male genetic link in autism

Scientists looking at the effects of mobile phone microwave frequencies on sperm have been conducted in rats, mice, and rabbits using mobile phone RF exposure for variable lengths of time. The results of these studies have shown that RF-EMR decreases sperm count and motility

and increases oxidative stress.(114) Genotoxic effects on sperm have also been found.(116) If autism is linked to aging sperm with presumably more genetic damage it is possible cell phones and wi fi from different sources could contribute to autism spectrum disorders.

Agarwal reported in Sterility and Fertility journal in 2009 the effects of one hour of cell phone RF-EMF on human sperm. He found a significant decrease in sperm motility and viability. He concluded that radiofrequency electromagnetic waves emitted from cell phones may lead to oxidative stress in human semen and cautioned against men putting their cell phones in trouser pockets. (115)

Mailinkot in 2009 looked at effects of RF-EMR from mobile phones on free radical metabolism and sperm quality. He exposed rats to a mobile phone for 1 hour continuously per day for 28 days. The study showed that "rats exposed to RF-EMR exhibited a significantly reduced percentage of motile sperm. Moreover, RF-EMR exposure resulted in a significant increase in lipid peroxidation and low glutathione content in the testis and epididymis." (113)

Avendano was the first to evaluate the effect of laptop computers receiving wireless Internet signals on human spermatozoa. Researchers evaluated semen samples from 15 men. "The samples were separated into 2 incubation groups: one that was exposed to a laptop computer receiving a WiFi signal for 4 hours, and another that was not. Despite the fact that the 2 groups were kept at a controlled temperature (25 °C) to rule out thermal effects, the results showed significant DNA damage and decreased sperm motility in the laptop-exposed group." (116)

Neurodevelopmental Disorders with Cell Phone Use

Animal and human research is now finding neurodevelopmental and neurologic abnormalities that are of serious concern especially considering the near universal use of cell phones and wireless devices inside and outside the home.

A study performed on adult rats showed altered behavior after 3 days of continuous exposure to cell phone radiation. They expressed stress behavior actions. (125) In another study the rats were exposed to a longer period of intermittent cell phone radiation. "Healthy male albino Wistar rats were exposed to RF-EMR by giving 50 missed calls (within 1 hour) per day for 4 weeks, keeping a GSM (0.9 GHz/1.8 GHz) mobile phone in vibratory mode (no ring tone) in the cage. Results showed passive avoidance behavior was significantly affected in mobile phone RF-EMR-exposed rats … when compared to the control rats. Marked morphological changes were also observed in the CA(3) region of the hippocampus of the mobile phone-exposed rats in comparison to the control rats. They concluded mobile phone RF-EMR exposure significantly altered the passive avoidance behavior and hippocampal morphology in rats." (126)

Rats exposed for even longer period-28 days- at peak power density of 146.60 μW/cm(2) showed that mobile phone radiation could affect the emotionality of rats without affecting the general locomotion. (127)

Another EMF rat study showed increased oxidation in the hippocampus which is key to memory and learning.(128)

Danish Studies Find Surprising Link between EMF and Behavior

Some studies have explored human behavior problems and cell phone use. (122)(123)(124) Two large Danish studies of 13,000(2008) and 28,745 children(2012) demonstrated that cell phone use was associated with behavioral problems at age 7 years in children, and this association was not limited to early users of the technology. Exposure to cell phones prenatally-and, to a lesser degree, postnatally-was associated with behavioral difficulties such as emotional and hyperactivity problems around the age of school entry. The results were a surprise to the authors who expected to find no effect

Autistic Behavior With In-Utero Exposure

Adid in 2013 was the first to demonstrate biochemical changes similar to autistim in rats exposed prenatally to cell phone radiation. "Mice exposed *in-utero* were hyperactive and had impaired memory… recordings of miniature excitatory postsynaptic currents (mEPSCs) revealed that these behavioral changes were due to altered neuronal developmental programming. Exposed mice had dose-responsive impaired glutamatergic synaptic transmission onto layer V pyramidal neurons of the prefrontal cortex. **We present the first experimental evidence of neuropathology due to *in-utero* cellular telephone radiation. "(129)**

Summary

The delicate and complex wiring of the brain is especially vulnerable to toxic exposure during early development. There are animal models demonstrating that autism can be created prenatally by exposure to drugs such as valproic acid, thalidomide, misoprostol, maternal rubella infection and the pesticide chlorpyrifos. (138) This is proof of principle and opens the door to further investigation of toxic interactions in autism.

Scientists believe neurodevelopmental disorders such as autism have common biochemical markers that may vary in subsets. These include reactive oxygen species, glutathione reduction, mitochondrial disorders, inflammation, DNA alterations with now hundreds of associated gene mutations. Some DNA changes are inherited but others occur de novo.

Autism it appears is not a single disorder, but a range of disorders that may have a variety of causes. While autism may have inherited genetic alterations there is a significant environmental component. Toxins such as heavy metals, industrial chemicals, food additives, pesticides, plastics, endocrine disruptors such as Bisphenol A as well as non-ionizing microwave radiation found in wireless devices can also cause cellular and molecular damage with production of reactive oxygen species, inflammation and genetic damage similar to that seen in autism. These toxins could act in concert to cause an array of biochemical and behavioral manifestations.

Unfortunately as we are increasingly exposed to the classic toxins there are novel insults to our cells from newer environmental factors such as nanoparticles in consumer products and wireless devices whose non-ionizing radiation which we now know can cause adverse biologic and

therefore health effects. Genetically modified foods create genetic pollution and are another area of increasing concern with regards to both human and environmental health.

It is difficult to sort out any one cause of autism or host of other modern diseases. In order to protect public health a rational and responsible approach to environmental toxins would be to apply the precautionary principle. If an environmental factor has been shown to have toxic effects with a reasonable amount of scientific data efforts to prevent commercial use or to reduce or eliminate that factor would be addressed rapidly and without excessive corporate or political interests that could obstruct responsible action. A systematic approach and ethical leadership is called for.

The Precautionary Principle in the EU

As per Article 174(2) of the European Community Treaty the precautionary principle is one of the fundamental principles of the European Union governing policies related to the environment, health and safety. The precautionary principle or precautionary approach states that if an action or policy has a suspected risk of causing harm to the public or to the environment in the absence of scientific consensus that the action or policy is not harmful, the burden of proof that it is *not* harmful falls on those taking an action.

Environmental scientists propose the precautionary principle as a new guideline in environmental decision making. It has four central components: taking preventive action in the face of uncertainty; shifting the burden of proof to the proponents of an activity; exploring a wide range of alternatives to possibly harmful actions; and increasing public participation in decision making. (136)

"Children today are surrounded by thousands of synthetic chemicals. Two hundred of them are neurotoxic in adult humans, and 1000 more in laboratory models. Yet fewer than 20% of high-volume chemicals have been tested for neurodevelopmental toxicity." Dr. Philip Landigan, Children's Environmental Health Center, Mount Sinai

Scientific Recommendations: Prevention of Developmental Neurotoxicity (133)

1) Legally mandated testing of existing chemicals and pesticides in commerce with prioritization of those with the most widespread use

2) Legally mandated premarket testing of new chemicals or processes before they enter commercial use

3) Prioritize those chemicals/processes that have neurodevelopmental toxicity

4) Develop a new clearinghouse for neurotoxicity as a parallel to the International Agency for

Research on Cancer to assess industrial chemicals and processes with emphasis on precaution and not absolute proof.

5) Shift from Risk Assessment to Alternatives Assessment as a more precautionary approach (135)

6) Reevaluate the international standards for non-ionizing microwave EMF in wireless communications to include biologically relevant safety limits that coincide with current literature on levels that do not cause human, animal or environmental harm. (134)

Autism Part 3 will explore the link to other potential environmental factors that may contribute to the sharp increase in this disorder.

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