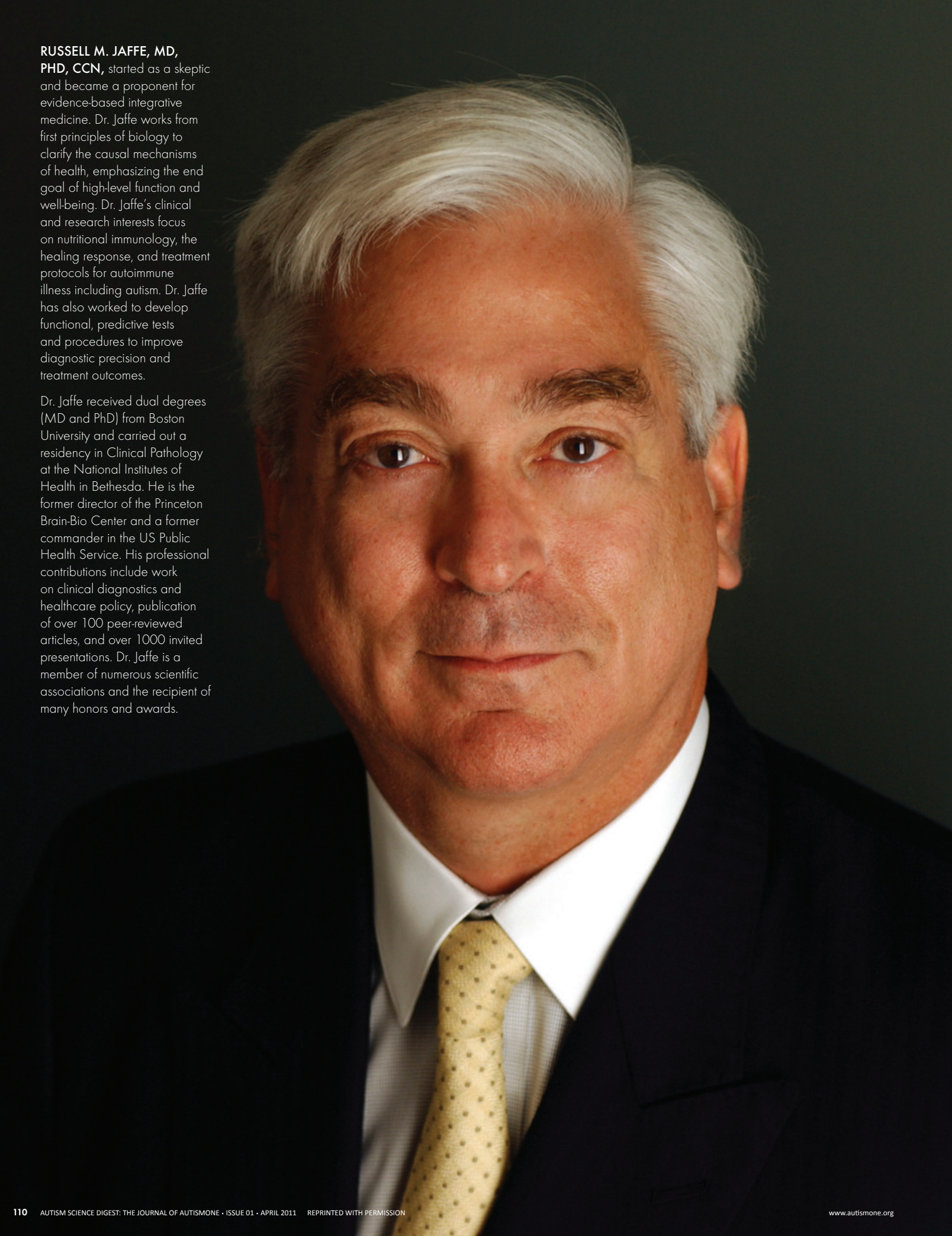

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GLOBAL ALERT:

ANTHROPOGENIC INFLUENCES ON BIOLOGY AND THE BIOTA, AND CONNECTIONS TO AUTISM SPECTRUM DISORDERS

BY RUSSELL JAFFE, MD, PHD, CCN AND NORMAN SCHWARTZ, MD

"No nation is any healthier than its children."

Harry S. Truman (1884-1972, 33rd president of the United States)

INTRODUCTION

Autism spectrum disorder (ASD) is one of several neurodevelopmental disorders that have increased over 100-fold in less than a century, particularly in the developed world.[1] Over this time period, an unprecedented two-way experiment between humans and the natural world has been under way.[2] As human activity reaches the point where it is affecting planetary ecosystems, the sum of local human choices has delivered unforeseen consequences often extending far beyond their source.[3] The outcome of this neither controlled nor blind experiment raises questions about the quality, diversity, and sustainability of life on earth.[4-28]

This article rethinks conventional understandings of autism from a multidisciplinary, integrative, and functional perspective, drawing on the disciplines of integrative physiology, molecular biology, environmental toxicology, and systems dynamics. Focusing on molecular causes of autism, we lay the foundation for a typology of ASD that differentiates between biochemically and metabolically distinct subgroups. This approach recognizes that clinical expressions of ASD are diverse, and that ASD possibly and more appropriately might be considered a collection of discrete disorders with some overlapping clinical expressions. When people with ASD are studied as a single group (as is typically done), important differences for one subgroup may not be apparent. However, development of better treatments for ASD depends upon accurate diagnosis.[5,6] Teasing apart possible ASD subgroups may allow for improved diagnostic precision and, ultimately, better therapeutic outcomes.

MULTIDISCIPLINARY PERSPECTIVE

"By seeking and blundering we learn."

Johann Wolfgang von Goethe (1749-1832)

In this report, we use functional insights of physiology[7,10-15] developmental biology[6-9], toxicology,[8,28] and systems thinking[9,10,15-18] to develop a proposed typology of ASD.[11] These four disciplines combine in what can be referred to as integrative science.[12-21]

Integrative physiology: Includes insights of molecular biology[13,14] and non-equilibrium thermodynamics[15] as they describe observable, macroscopic phenomena and behaviors.

Molecular biology: Explores living systems from molecules to macro compositions of chemicals[16,17] seeking insights into higher order functions.[18-25]

Environmental toxicology: Examines the effects of low levels of pervasive xenotoxins, with a particular focus on times of special vulnerability to xenotoxic effects (e.g., gestation, early childhood development, moments of intense distress). Individual vulnerability varies based on efficiency and resilience of cell systems.[6-9,19]

System dynamics: Uses an interdisciplinary and holistic[20] perspective to look at components interactions and the timing of their interactions[21] (in contrast to mechanistic and reductionist biomedical views that look at single variables or isolated variables).[20,26]

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In addition to his medical degree and residency training, Dr. Schwartz has received postgraduate training and education from the American Academy of Environmental Medicine, the Santa Fe Institute for Complex Studies, the Functional Medicine Institute, the International College of Integrative Medicine, and the American Academy for the Advancement of Medicine. He is a founding member of the American Society of Integrative Medical Practice and a Fellow of the Health Studies Collegium, a health policy and clinical outcomes research foundation.

When collective life on earth and in the biosphere is appreciated as a super organism that continually reacts and rebalances itself, it becomes apparent that how organisms interact and influence the environment affects their health and their offspring's sustainability.

INTERDEPENDENCE WITH ALL LIFE

"Survival of a complex system (cell) is constrained by the *least* available essential item."

Russell Jaffe (1947-), biotechnologist
(based on Justus von Leibig, 1803-1873)

People are to the environment as fish are to water, which is to say, interdependent. Physiologic systems are also remarkably resilient, as complexity theory,[22] systems dynamics,[23] and informatics[24] has helped understand. Cooperation occurs at multiple interconnected levels to ensure rapid responses to internal and external stressors to maintain homeostasis.[25-47] Wherever we look in detail, myriad interconnections between living systems and the biosphere are observed.[26-36] For example:

1. The water we drink has been recycled and purified for eons inside earth aquifers.[32]
2. The air we breathe is exchanged globally with all other respiring organisms.[27,35,43]
3. The essential nutrients within us are recycled through soil with remarkable efficiency and lack of waste.[10,14,42]
4. Conserved biochemistry across all cellular life includes metabolic control points that show special vulnerability to toxins at certain times.[34]

Life is self-organizing, exhibiting properties of complex adaptive systems that operate far from thermodynamic equilibrium. Organisms must maintain local coherent autonomy and global connectivity over 16 orders of magnitude in space and time to achieve a healthy, dynamically stable state. From a biomolecular standpoint, these properties of biological systems often emerge only at quaternary or architectural levels of organization.[28-34] This means that functions and properties in complex systems[25,29] are unpredictable from understanding lower levels of organization.[30] Complex functions include the exquisitely balanced neuroimmunohormonal, reproductive, catabolic recycling, and anabolic rebuilding processes upon which life depends. A common energy source and structure that distinguishes life from inert matter drives these processes.[19,32-34]

The extent to which ecosystems and organisms are able to maintain stability and homeostasis is intimately related to the quality of the environment. We now know that the fitness of the planet to support life is not a stable state but is actively maintained far from equilibrium by interdependent life forms sharing the same atmosphere, hydrosphere, and lithosphere.[16-31] This interdependence of biota (the total collection of organisms) means that harm in one locale can have wide-ranging consequences elsewhere. If we view biology as a grand synthesis, regulated by interdependent self-sustaining mechanisms, it is clear that study of isolated parts can yield only limited information. Systems approaches that use holistic tools will yield more useful information and, in this instance, can provide insights into the causes and management of pervasive developmental disorders (PDDs), including ASD.[32]

BEYOND PREDICTABLE LIMITS

Biology builds elegant complexity from simple fundamental building blocks.[32] Myriad agents interact over multiple levels of organization, and a unifying theoretical understanding to elucidate basic principles is still emerging. Until the last few decades, the biological and medical sciences were largely phenomenological in approach, based on observation and experiments leading to description and categorization. A very small percentage of this "medical science," observational at best, has passed rigorous scientific scrutiny. In fact, the US Congressional Office of Technology Assessment found that 87% of general medical practice is validated only by consensus, and not by peer-reviewed evidence.[33] Lewis Thomas, in his essays on "The youngest science" as well as Sir William Osler a century before in his *Aequanimitas* essays tackle the same theme.[34,35]

Science proceeds by describing and explaining, leading to testable predictions. Although the past several decades have produced a large body of data describing the state of our biosphere, how one assesses the fitness of the environment is central to how one shapes a response. Whereas traditional environmental models use genetically determined, reductionist reproductive success as the criterion for determining fitness, systems biology understands that organisms alter ecosystems *other* than through simple genetic inheritance known as epigenetics.[36] When collective life on earth and in the biosphere is appreciated as a super organism that continually reacts and rebalances itself, it becomes apparent that how organisms interact and influence the environment affects their health and their offspring's sustainability.[37-47] Living systems' resilience and capacity for homeostatic self-regulation can successfully handle environmental toxins only up to a finite limit.[32,40,38]

As human activity pushes ecological and biological boundaries beyond predictable limits,[39] clinical[40] and epidemiologic observations are documenting some of the consequences. For example, as environmental toxins disperse and interact in waterways, soil and air, ecosystem disruptions result.[41-51] These disruptions have proved challenging to calculate and accurately model; however, conservative estimates include an 8.8 year average reduction in life span due to toxic minerals and related toxins alone, without taking into consideration other xenotoxins. The incremental medical cost from toxic minerals is calculated to exceed $100 billion annually (R. Sanawane, personal communication, 2006).

GLOBAL ALERT

"A new consciousness is developing that sees the earth as a single organism, and recognizes that an organism at war with itself is doomed."

Carl Sagan (1934-1996)

Healthy systems are resourceful, interdependent, variable, and resilient. When these complex systems become distressed, their responses become fixed or rigid, increasing the risk of system overload, collapse or failure.[42] In 1998, an international team of Earth scientists defined nine fundamental planetary biophysical systems, and also defined boundaries within which the systems could function successfully and beyond which progressive harm to living systems would occur.[43] They also made clear that transgression of one boundary adversely affects resilience in other life forms.

For three of the nine systems delineated by that team of scientists, boundary conditions have already been exceeded.[44] The consequence of concurrently transgressing multiple boundaries enrolls living systems in the unprecedented experiment described in the introduction. The three affected systems include:

1. **Biological diversity:** The planet is experiencing a dramatic increase (by two to three orders of magnitude) in species loss, with rates between one hundred and one thousand species lost per million species per year (versus the natural background rate of one loss per million species per year).[45]

2. **Nitrogen cycle:** There is a greater than 100% deviation in the nitrogen cycle from historical levels.[46]

3. **Climate change:** Carbon dioxide concentrations are approaching the danger zone of 400 ppm, resulting in climate change that makes it possible to kayak at the North Poll in January (as was done by MIT astrophysicist Sara Seager in 2008).[47]

EXPLORING THE ETIOLOGY OF AUTISM

> "…That a disease is complex or multifactorial does not imply that simple solutions cannot be found or that clinical advances following insight cannot be swift."
>
> JA Rees (Science, 2002;296: 698-701)

Reproductive, neurodevelopmental and learning disabilities have rapidly increased over the past century.[48] One in five children entering kindergarten currently carries a mental health diagnosis,[49] representing a tenfold increase within one generation. As shown in Figure 1, the rate of increase in autism has steadily risen since 1992. Over the most recent 2-year period, the Centers for Disease Control and Prevention (CDC) documented an increase from 1 in 15 to 1 in 10 students diagnosed with attention-deficit hyperactivity disorders (ADD/ADHD), and an increase in ASD from 1 in 150 to 1 in 110 children (Figure 2).[46-50] Autism is also growing faster than other developmental disabilities (Figure 3, next page).

Where ASD is concerned, evidence continues to accumulate that environmental factors play an important and potentially causal role in its etiology.[50] This article offers a straightforward set of interdisciplinary concepts and relationships that associate the rising epidemic of neurodevelopmental disorders[51] to exposure to multiple toxins at vulnerable times.[52,53]

Where ASD is concerned, evidence continues to accumulate that environmental factors play an important and potentially causal role in its etiology.

Figure 1: Autism increase 1992 - 2009 (%)

Note: Cumulative growth in autism cases by percent (%) suggests that *rate* of increase continues to rise.

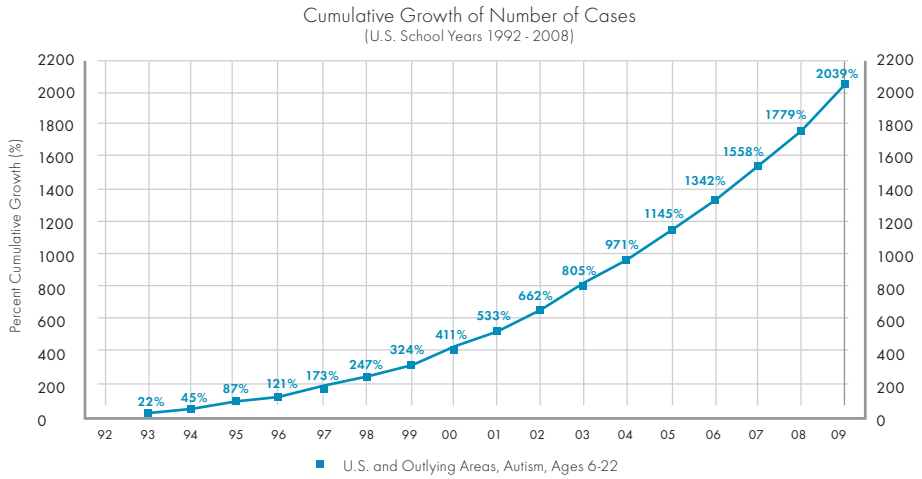
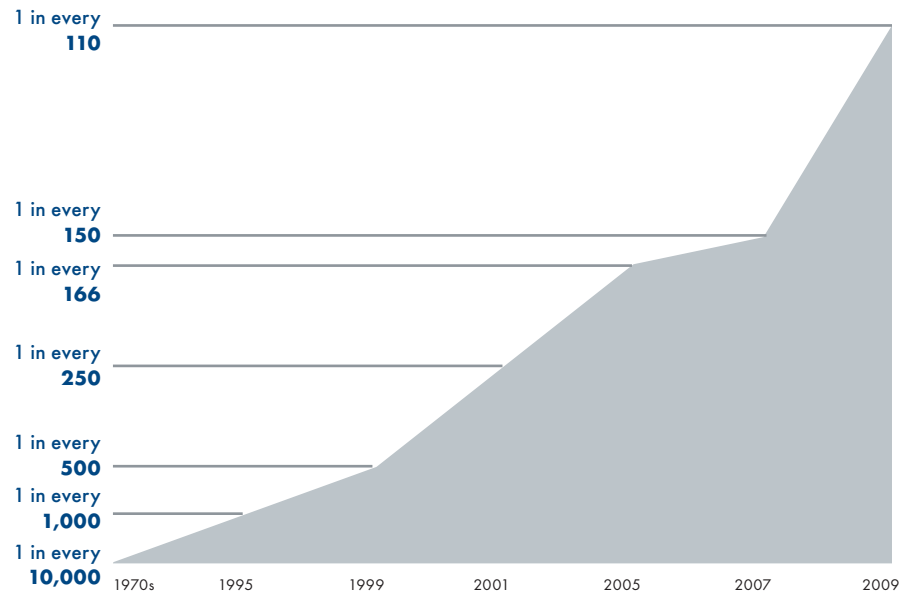


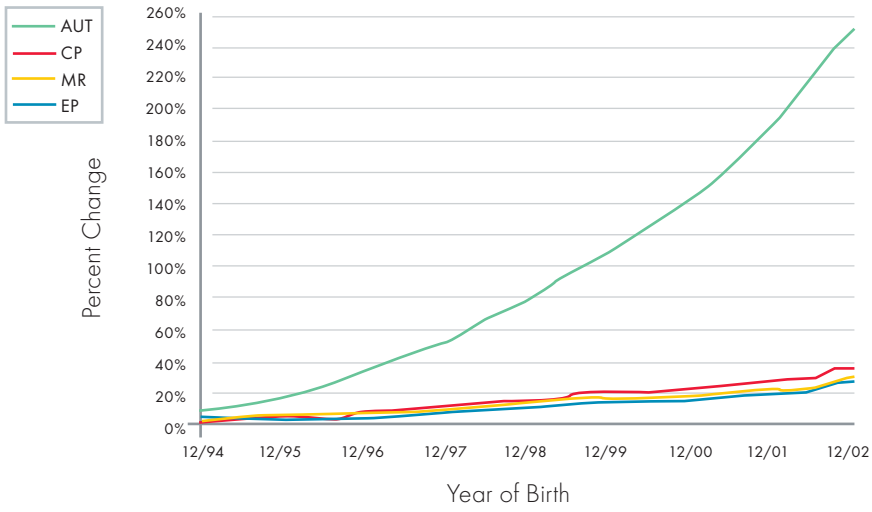
Figure 2: Change in autism frequency over time



Particularly implicated are substances known as xenotoxins, which cause oxidative damage[54] to vulnerable cell components through free radical generation and concomitant depletion of protective antioxidants such as tocopherols,[55] ascorbate,[56] glutathione,[57] and coenzyme Q10.[58] Xenotoxin exposures are particularly pernicious when the affected organism is also experiencing a deficit of essential nutrients.[25-31]

In addition to xenotoxins, a number of other environmental influences affect growth factors[59] and development. These include:

Figure 3: Percent change in all disabilities: Autism growing faster than other developmental disabilities (1994-2002)



[Source: California Department of Developmental Services (DDS). Figure 2 from *Autism Spectrum Disorders: Changes in the California Caseload: An Update:* 1999-2002. Sacramento, CA: California DDS, 2003]

- **Genetic** and **epigenetic**[60] **adaptive polymorphisms**,[61] particularly those that regulate cell communication and transport through methylation, sulfur metabolism[62] and related detoxification[63] competences.[64]
- Dopamine and other **neurotransmitter signaling**.[65]
- **Neural network formation** and resilience, which is important for the development of integrated somatosensory information processing and communication systems.[66]
- **Antigens** presented to the developing intestine through breastfeeding or formula, and timing of food introduction in relation to gut maturation.[67]

DESTRUCTIVE IMPACT OF XENOTOXINS

"It is not the strongest species that survives, nor the most intelligent, but the one most responsive to change."
Charles Darwin (1809-1882)

Xenotoxins include five groups: Toxic metals[68,69] (TMs), volatile organic compounds[70] (VOCs), persistent organic pollutants[71] (POPs), electromagnetic fields (EMF), and radioisotopes. The destructive impact of xenotoxins occurs because all five classes of toxins operate as oxidative and metabolic disrupters of biological control systems.[72] Indeed, at currently observed exposure levels, methylmercury,[73,74] lead,[75] and paraquat[59-61] oxidize progenitor cells by synergistic mechanisms. This disrupts cell-signaling pathways involved in cell division and other core cell functions.[76] Other toxic metals[77] and biocides may have similar mechanisms of action, as they are known free radical generators *in vitro*.

The five classes of xenotoxins—which are largely anthropogenic (i.e., man-made) in origin—are circulating in the environment at three or more orders of magnitude more than just a century ago. In many cases, this means that biological systems must respond to 1,000 times more of a given toxin. Moreover, xenotoxins and their oxidation products tend to bioaccumulate and recycle in the environment.[78]

The absence of available data cannot be taken to signify an absence of risk. Of the over 100,000 chemicals currently in commercial use, less than one percent have been studied in any detail, and fewer than 40 have been studied in regard to interactions. However, hundreds of xenotoxins have been found in samples taken during the second or third trimester of pregnancy, as well as from umbilical cord blood taken after birth.[79] Alongside accumulating evidence that uptake of toxins from the environment may be greater during pregnancy and nursing, a body of evidence links exposure to xenotoxins at vulnerable times during gestation and early childhood development to increased risk of ASD and PDD, as well as other developmental and learning disorders.[80]

Unfortunately, oxidative stresses reduce nutrient density in the diet, at the same time that the need for nutrients is increased due to enhanced free radical activity. In a negative cycle, maternal deficits in essential nutrients lead to lessened ability to exclude or detoxify toxicants.[81] The body becomes so hungry for what it lacks that it becomes less discriminating in intestinal uptake. For example, when the body lacks zinc[82,83,84,85] and magnesium,[86] it will take up more pro-oxidant toxic metals such as lead, mercury,[88,89,90] arsenic,[91] cadmium,[92] and nickel.[93]

When present together, xenotoxic effects are typically multiplicative and synergistic, rather than additive and linear as previously assumed.[94] Moreover, toxins are often more potent when the environment is more acid (versus in a healthier alkaline state). This is partly due to depletion of needed buffering minerals and more rapid consumption of protective antioxidants,[95] which leads to loss of repair. Over time, cumulative repair deficits (conventionally known as inflammation) become markers of additional disability and degenerative illness.[96] Endogenous detoxification systems become overwhelmed by toxic waste matter, above the level that can be rendered more soluble and less toxic while in transit for excretion.

Methylation pathways are important for detoxification and transport pathways.[97] Homocysteine is a functional marker of methylation detoxification pathways. When cells shift into survival or "essential only" mode (rather than the "thrival" mode of healthy cells), protective genes are repressed until the cells recover from their low-energy,[98] essential nutrient deficit condition. Although this shift to survival mode is an adaptive response,[99] one consequence is that elective protective molecules like metallothionein and melatonin (which protect from toxic minerals) are no longer produced.

All of this suggests the importance of reducing toxin exposure during pregnancy and enhancing physiologic competence,

The absence of available data cannot be taken to signify an absence of risk.

...It is clear that xenotoxic **TMs, VOCs, POPs, EMFs, and radioisotopes disrupt biological processes** in multiple, synergistic ways, and deplete essential protective antioxidants and buffering minerals.

through mental and physical exercises, safe and adequate nutrition,[100] and supportive family structures.[101] More specifically, a positive cycle should include sufficiency of essential nutrients reflected in predictive markers, thus recognizing biochemical individuality. This cycle would also include mental and physical activities sufficient to provide stress resilience. The final element of this positive cycle is relationship to others and the environment that includes stewardship and meaningful work, providing the basis for resilient self-esteem, optimism today, and hope for tomorrow. This can be synthesized as the Alkaline Way for sustainable living.

FURTHER LINKS TO ASD

The persistence of and interaction among newly synthesized chemicals with toxic effects raises several concerns. First, there is an alarming **absence of adequate developmental neurotoxicity testing.** In general, chemicals introduced into the environment have been assumed to be safe unless or until harm is established with a high level of scientific consensus. This approach has proven costly to both life forms and social structures. Subtle yet profound effects from modest levels of persisting toxins are increasingly found,[102] which supports a precautionary principle approach. The burden of demonstrating safety should be placed on that which is novel, rather than assuming innocence for the "latest and greatest."

Second, the **inability to adequately monitor pollutants**, when the levels that cause harm are below the detection limits of generally available equipment, is a serious shortcoming. In this area as well, it would be more sensible to adopt a precautionary approach, placing the burden of establishing safety on the source of novel compounds with regard to long-term or systemic effects.[103]

Third, it is clear that xenotoxic **TMs, VOCs, POPs, EMFs, and radioisotopes disrupt biological processes** in multiple, synergistic ways, and deplete essential protective antioxidants and buffering minerals. Xenotoxins can also result in the following negative outcomes:

A. Decreased ATP and decreased production of other high-energy compounds in the mitochondria.[104] This results in reduced energy for key elective cellular processes such as repair, digestion,[105] detoxification, immune[106] and neurohormone functions, and synthesis of elective protective products.[107] All these processes are sacrificed when the cell energy drops, as marked by a reduction in the ATP/ADP ratio of less than 100. Whereas healthy cells have an abundance of potential energy stored in ATP to apply to any cell need, a loss of this reserve potential shifts cells into survival mode until cell energy is rebuilt.

B. Enzyme inhibition. Inhibition of enzymes by toxins disrupts cell equilibrium that depends upon enzyme catalysts. Metabolic control systems, digestion, nutrient assimilation, detoxification, and neurohormonal regulation all become disintermediated.[108]

C. Oxidative damage. Depletion of protective antioxidant defenses[109] such as ascorbate leads to an unhealthy increase in the cell reduction-oxidation (or redox) potential, which, in turn, leads to an increase in the risk of oxidative damage. This also means that the proton gradient between the cell cytoplasm and the mitochondrial[110] battery is reduced,[111] causing further declines in ATP energy production.[112] This then increases the risk of a shift to survival mode away from healthy elective synthesis.[113] Studies of exposure levels to chemically diverse toxicants common in industrial societies also confirm that increased oxidative stress results in essential nutrient deficits and disruptions in critical cell signaling pathways.[114]

D. Cumulative repair deficits. Inflammation[115] (or cumulative repair deficits) means that exposure to xenotoxins is occurring above levels that can be detoxified. Cumulative repair deficits and deficits in needed nutrients are sufficient to cause disability from repair defects. In the fetus or developing child, this inflammation may contribute to ASD[116] and PDD risk.[117]

E. Bioconcentration. As detoxification ability falls, bioconcentration of toxic matter rises. Whereas cell systems usually have half-lives or turnover measureable from fractions of a second to days, toxins of concern have half-lives or turnover in the environment from months to millennia.[118]

F. Autoimmunity. When toxins bind to cell proteins, their conformation and function are altered. This can render them foreign to the body, provoking autoimmune responses.[119] Autoimmunity contributes to chronic and degenerative illness. Aspects of ASD and PDD may be autoimmune[120] expressions during gestation and childhood development.[121] Loss of homeostasis during gestation and early life can also disrupt core immune communication systems, as observed in some cases of ASD and PDD.[122] (In the elderly, loss of homeostasis can manifest as hypertension and hypercoagulation syndromes, with an increase in heart attack and stroke, accelerated aging, and loss of innate anti-cancer surveillance.)

CHILDREN ARE NOT LITTLE ADULTS

> "Children's exposure to chemicals at critical stages in their physical and cognitive development may have severe long-term consequences for health."
>
> International Program on Chemical Safety, WHO, ILO, UNEP (2011)

The exquisitely poised and finely tuned process of brain development is continuous from embryonic development through the life span.[123] Under usual circumstances, neurodevelopmental functions operate so well that their adaptive and self-correcting nature is easily overlooked or taken for granted. However, the complexity, sensitivity,[124] connectivity, plasticity,[125] and development of the human nervous system are vulnerable to dysfunction and interference at each stage of development.[126] In addition, the developing or remodeling brain is more vulnerable than the stable brain. Children's metabolic and detoxification systems have less reserve than those of adults, when corrected for weight differences, increasing children's vulnerability to multiple, intermittent toxic exposures. For better and for worse, childhood behaviors interact with and are more exposed to the environment.[127]

... The developing or remodeling brain is more vulnerable than the stable brain.

ELEGANT FUNCTIONAL COMPLEXITY

"Our task must be to free ourselves by widening our circle of compassion to embrace all living creatures and the whole of nature and its beauty."

Albert Einstein (1879-1955), Nobel laureate in Physics

The human brain has an average of 10^{21} molecules, and performs an estimated 10^{16} operations per second. This more recent and precise measurement is two orders of magnitude faster than previous estimates. The adult brain uses about 10 watts of energy, which represents 6.7×10^{-5} times *less* energy than a comparable super computer. (The 120,000 processors in the super computer Blue Gene achieved a comparable speed in 2008[128] while consuming 1.5 megawatts of power.) The incredible efficiency of the human brain is achieved through massive parallel processing resulting from the interconnections of nerves and the catalytic power of enzymes. Additional processing capacity may come from discrete piezoelectric collagen fibrils, insulated by glycosaminoglycans that wrap around each fibril.

This astounding neural connectivity requires an intricate process of successful sequencing and synchronization in the seven following areas:

1. **Differentiation** of stem cells into progressively more specialized nerve cells,[129]
2. **Proliferation** to replace unneeded or worn-out cells by apoptosis (programmed cell death),[130]
3. **Migration** to go where needed or where the milieu is more favorable,[131]
4. **Axonal** extension to connect and reach out,[132]
5. **Synaptogenesis** to allow nerves to connect and interconnect,[133]
6. **Gliogenesis** to protect and repair nerves,[134] and
7. **Myelination** to insulate nerves and facilitate information flow.[135]

These delicate processes enable the human nervous system to respond **visually** to a single photon in both the retina and the enterocyte; respond **auditorily** at near quantum molecular vibration thresholds in the ear and with similar sensitivity to **neurochemical oscillations** in the gut-associated lymphoid tissue (GALT);[136] distinguish the **smell**[137] or **taste**[138] of a substance based on a handful of molecules; sense minute **pressure changes** in the skin and in the tentorium covering the brain;[139,140] and perceive **sound intervals** as brief as a millionth of a second between left and right ears.[76] Since the introduction of xenotoxins, interference with these systems has been inadequately studied, particularly as regards interactions among different toxic agents. The rising rates of ASD and PDD raise questions for which there are as yet too few answers. The increase in ASD has outpaced best efforts to increase available resources to understand and treat these conditions more effectively.

CONNECTING THE DOTS

"If we can grasp that we are the world we depend on, then we will find where we truly belong and get on with seeking a way to live in harmony within a rich, vibrant community of living things."

David Suzuki (1936-) and Amanda McConnell (1970-), *The Sacred Balance*, 2007

Based on the preceding discussion, we propose six ASD subgroups and six corresponding avenues of possible intervention. If confirmed, these subcategories would facilitate more accurate diagnosis through use of validated functional tests, and would enhance the likelihood of meaningful therapeutic outcomes. Each of the proposed subtypes has a distinct internal biochemical and external environmental milieu.

1. **Redox increase.** This reflects low cell vitality as a function of antioxidant electron carriers that are depleted and unable to prevent oxidative stress and free radical damage to systems that are performing development or repair functions.[141]

2. **Digestive competence.** This includes the ability to break down, assimilate, and eliminate what is taken in, and requires examining the entire digestive system, from prebiotics to probiotics, from mucins to secretory IgA, from metallothionein to bile acids, and from stomach acid to pancreatic digestive enzymes.

3. **Anabolic/catabolic balance.** This reflects repair competences or their deficit, including neural and systemic unresolved inflammation.[142]

4. **Detoxification.** This pertains to the ability to safely convert toxins into more easily excreted and less harmful substances before delicate control systems are damaged.

5. **Somatosenory information processing and analysis.** Limited reserves can lead to system overload and entrainment of information processing.[143]

6. **Neuroimmunohormonal feedback integration.**[144] Neurotransmitter, immune and hormonal systems function as a single, integrated control system with cytokines as messengers.[145] (Jaffe has called attention to the complete parallel with "Governing Vessel" as described in traditional Oriental medicine.[146])

CONCLUSION

"The problem lies not in the intentions, nor in the dedication of individuals, but as so often in the history of science, from a limitation in the prevailing paradigm or model that governs and limits thinking in any given era."

Thomas Kuhn, PhD (1922-1996), Professor, Philosophy of Science

Autism spectrum disorders are a complex group of neurodevelopmental disorders near or at epidemic levels, particularly in the developed world. The causes remain unknown, and the clinical expressions diverse. The increase in 70 years from less than 1 in 10,000 to around 1 in 100 children (2010 estimate) is not explainable through genetics.

Because ASD typically affects multiple body systems, with altered function spanning virtually every level of biology and behavior, it can be challenging to deliver therapies that accurately match an individual's biological state. By comprehensively synthesizing physiology, molecular biology, integrative toxicology and systems dynamics, it is possible to come to a more functional understanding of ASD. With the goal of improving diagnostic precision and therapeutic outcomes, we propose six likely subgroups with distinct biochemical profiles and implications for best outcomes therapies. This proposed classification requires further exploration.

Autism research, to date, has been guided primarily by a reductionist, linear model that focuses on genetics, and considers single-variable, placebo-controlled experimental designs as the "gold standard." This approach has limited ability to capture epigenetic changes, and also implicitly presumes that ASD is a single condition with a spectrum of symptomatic expressions. When data averages for whole groups are taken, the distinctive characteristics of subgroups cannot be easily observed.

As stewards for the generations to come, and as physicians concerned about the suffering that ASD and PDD entail, we believe it is time to devote sufficient resources to test the validity of possible discrete ASD subgroups. In a future article, we will model an integrative approach and propose predictive markers for each subgroup.

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