Time to Get a Grip

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Does an environmental role in autism make sense? How do we decide?

And if environment *is* involved in autism, what do we do about it? These are challenging questions. Because our available information is complicated in many ways, each of us answers these questions based on our own judgment and deeply held worldviews.

We already know enough to take the environmental role in autism seriously. To say that the environment is involved in causing and triggering autism means that we believe that there have been new and different things going on in recent years, and that these developments have impact upon us. This is an easy claim to defend, and I will do that in this article.

To say that environmental factors can cause or trigger autism means that we have to look at the whole person and whole body, since environmental toxins and stressors will affect the whole body. This involves shifting from an older model that considers autism as a genetically determined "brain disorder" to a newer and more inclusive model that considers autistic behaviors as one of many effects of both genetic and environmental impacts on the whole person, including but not limited to the brain.[9]

This newer model of autism (or really, autisms, since there are many kinds of autism) implies that we have great opportunities to do constructive things about this challenge. To say that there are environmental causes and triggers of autism implies both that we can *prevent* the impairments associated with at least some kinds of autism, and that the suffering associated with at least some kinds of autism can be treated.

And finally, *it is time* for us to *get a grip* on this issue. If there is any chance at all that the autism of at least some people was *preventable* or is *treatable*, then *prediction* of risk, *prevention* of harm, and

reversal of injury all need to become top priorities. Moreover, environmental deterioration is a serious problem for everyone; understanding and handling it in autism may help many other challenges as well.

Why Autism and Environment?

It is often said that autism is the most highly genetic of the neurobehavioral disorders, and that there is little or no evidence of environmental factors.[28] However, observations about environmental factors relevant to autism go back decades, though they have been obscured in recent years by the dominance of a genetic focus. The view of autism as genetically determined is supported by observations of high "concordance" (matching autism diagnoses between identical twins) and high recurrence (increased chance of subsequent children having some kind of autism spectrum disorder after an autistic child is born into a family). In addition, a claim that autism is predominantly genetic rests on an assumption that our environment is stable and/or that we are not affected by environmental changes.

When we examine the frequently cited figure of a 90 percent "concordance rate" among identical twins (meaning that if one twin is autistic, there is a 90 percent chance that the other one will also be autistic), we can see that it overstates the case. Among identical twins, there is a 90 percent chance that if one twin is fully autistic, the other will have *some* autistic features, but only a 60 percent chance that the second twin will be *fully* autistic. While some researchers tend to focus on the 60 percent to make a case for genetic predisposition, we need to explain the 40 percent as well. To explain this nonconcordance we need to think about not just genes, but also the environment. Moreover, we also need to explain recent reports of high concordance among dizygotic (fraternal) twins, which suggest environmental rather than genetic factors.

We also know that the number of people diagnosed with autism has skyrocketed, both in the U.S. and in other countries. The current figures are running ten times higher than they were 15 or 20 years ago. The twin concordance data just discussed may not even apply to the new cases, since the studies were done before these increases were observed. Some say that the increases are merely due to better awareness and diagnosis of autism, or expanded diagnostic criteria. However, we would need solid proof of this claim in order to dismiss the possibility that something new, different and harmful is going on with our children—and such proof does not exist. Autism increases point to a role for the environment, since genes don't change that fast. The uncertainty and debate have not excluded the possibility that at least some portion of the increase in diagnoses is real. This gives us the responsibility to apply our serious and focused attention and resources to addressing what may be causing these alarming trends and what we can do about them.

The Big Picture: Major Environmental Changes

Let us now zoom out from autism and look at the bigger picture. If we assume that autism is mainly or purely genetic and not environmental, we are implying that nothing has changed in the environment that would alter genes or the ways that genes are expressed. Can we really defend the claim that the environment is stable? Hardly. Consider the following sample of unprecedented problems:

- In the past century there has been an exponential rise in the invention and production of new chemicals never before seen on the planet earth. Many of these are noxious and toxic by design (e.g. pesticides, industrial solvents), and many others have unanticipated toxic effects.
- We are facing a rise in a multitude of human illnesses including cancers as well as chronic, allergic, immune, autoimmune and degenerative illnesses.
- Among animals we are seeing a rise in infectious and cancerous illnesses and in malformations.
- We are losing biodiversity, with the greatest rate of extinction of plant and animal species since the Age of the Dinosaurs, not to speak of great loss of cultural diversity including the knowledge bases underlying many ecologically adaptive health-promoting traditions.
- There are a growing number of dead zones in the coastal oceans near large population settlements. Ocean pollution is enormous and we are seeing the dying out of fish stocks.
- Global climate change is becoming undeniable and appears to be proceeding faster than anyone had anticipated even a few years ago.

Addressing these and many more changes, a Millennium Ecosystem Assessment of the magnitude of the interlocking environmental crises we face was authored by more than 1,300 scientists from 95 countries and published early in 2005 by the United Nations and multiple partner organizations from around the world (www.millenniumassessment.org or www.maweb.org). Their "bottom line" summary sentence states, "We are spending Earth's natural capital, putting such strain on the natural functions of Earth that the ability of the planet's ecosystems to sustain future generations can no longer be taken for granted." From the vantage point of all of these unprecedented changes, there is no way to defend the claim that our environment is stable.

Given this pervasive environmental instability, we must ask ourselves, "Why would human children, and their developing brain and bodily systems, be spared?" In fact, given their delicacy, there is every reason to expect that children and their developing brains and bodies will be particularly affected.

Health Impacts of Environmental Change

Even in the face of widespread changes on our planet, some will still argue that there is uncertainty about whether these changes have health effects, as well as whether they could be causing or triggering autism. Is this a strong enough argument to justify inaction or delay? Not really. In committing to take notice and action, it is key to remember the saying, "Absence of evidence is not the same as evidence of absence." That is: a) just because something hasn't been thoroughly studied doesn't mean that nothing is going on, and b) the way you design a study has a big influence on the results you get.

Particularly important here is that we are learning many new things about how environmental exposures act upon our bodies that are forcing us to re-think how we decide what is safe and what is not safe. Michael Lerner discusses this "revolution in environmental health sciences" in his article, "Letter to a Friend Who Cares," which is in this issue. Two major areas of change are 1) how we define a "safe" level of exposure, and 2) what happens when we have many exposures in combination.

"Safe" levels: Recent science is showing us that chemicals at very low doses, many times beneath the previous "safety" thresholds, can cause harm—not by *killing* cells or living beings, but by mechanisms like *biomimesis—mimicking* the body's or organism's own signaling molecules. The most famous example of this is "endocrine disruption," in which chemicals such as those in pesticides or plastics can, in very small doses, act like hormones, and confuse the body's hormone regulation systems (for more information, see www.ourstolenfuture.org). Many people think that this might be relevant to autism, given that so many more boys than girls are affected and an altered hormonal environment might affect vulnerability.

Exposures in combination: We also are learning that combinations of exposures can have effects that could never be predicted from studying each exposure by itself. For example, researchers recently studied three chemicals found in the water in Brick Township, N.J., where an autism cluster was discovered. Each of these chemicals was individually determined at that time to be below toxic thresholds. However, in this experimental study, all three together damaged a pathway in brain development that each alone (or even in pairs) did not do.[19]

Together, these new scientific developments mean that we have probably hugely underestimated the health and ecological risks from environmental exposures.

We Are All Polluted

While it is surprising how little our "body burden" of chemicals has been studied, measurements show that we are all walking around with traces of at least hundreds of chemicals in our bodies. Even more alarming, babies are now *born* with traces of hundreds of chemicals in their bodies (for more information, see the October 2006 issue of *National Geographic*). Given the new science showing that chemicals in low doses and in combinations may have significant effects that can't be predicted from studying higher doses of single exposures, it appears that we are basically all living in uncharted territory regarding the health impacts of pollution in our own bodies.

Many Other Changes in Our Ways of Life

Chemicals are not the only new environmental exposures that we face. Many other exposures and stressors have emerged or greatly increased in the past century, including:

- Industrial farming: processed and refined foods; chemical pesticides and fertilizers; genetically modified foods
- Reproductive and hormonal manipulation
- The information revolution: media, computers and "information overload"
- Electromagnetic and nuclear radiation
- New-to-nature drugs, which may have long-term effects that take time to detect and would thus be missed in the standard short clinical trials that precede marketing
- Oral antibiotics, which change the ecology of intestinal microorganisms in unprecedented ways, and change the resistance properties of bacteria
- Air pollution and incineration disseminating many toxic substances—some new-to-nature
- Mechanically generated noise

It is possible to design studies in which any one of these changes is shown to have no significant effect in and of itself. However, it is also possible, and likely, that the combination of many of these exposures changes important aspects of our basic health. In this changed state, and particularly in the setting of genetic vulnerability, a further straw can break a camel's back. The impacts of combinations ofstressors are likely to be related to the rise in the number of people diagnosed with autism.[6]

Environment and Genetic Vulnerability

In the face of all of these environmental changes, we need to consider a different role for genes than outright determination of our health. Genes related to autism may not so much cause autism as set some people up to have greater vulnerability to factors that can trigger autism. This is a model of "gene-environment interaction," and it suits what we have learned to date better than a model of "genetic determination." Right now, we know of no genes that directly and inevitably cause autism. Even the genetic disorder Fragile X, which some people

describe as a "cause" of autism, is only associated with autism in 30 percent of cases, and therefore may be an extremely strong risk factor but still cannot be considered a "cause."

This "gene-environment interaction" model helps explain why it has been so hard to find "genes for autism." Some metabolic and signaling pathways are more involved with relating to the environment than others, and each such pathway involves many genes. The National Institute for Environmental Health Sciences is studying genes in such environmentally responsive pathways in its *Environmental Genome Project*.[20;30] Given the great variability in environments in which human beings have lived throughout our long history and migrations all over the planet, the many genes in these pathways are likely to show greater variability than other genes whose functions need to remain more stable across environments. We are already accumulating evidence of genetic differences in environmentally responsive genes, and environmentally responsive metabolic pathways in children with autism.[4;5;13;14;23] But any one environmentally responsive gene may have only a modest effect; and there may be many different combinations of such genes that lead to *vulnerability* to autism and a variety of exposures that alone or in combination may *trigger* the autism. This means we need fresh thinking about how we study genes and environment in autism. In particular this suggests that we need more study of environmentally responsive metabolic and signaling pathways, since these will guide us both to where to look for relevant genes, and also (to be discussed more below) to where to look for treatment targets. [11;13]

Can Regulation Keep Up With Science and Technology?

Currently, chemicals are studied only one at a time and there is no standard procedure for assessing low dose or combination effects. Moreover, a very large number of chemicals, those that were on the market before the institution of present regulations, have been "grandfathered" in, that is, allowed to be marketed without testing.

Amazingly, there is no requirement to test chemicals for their impacts on the developing nervous system, so that out of the approximately 3,000 chemicals produced in the largest volumes, *only 20-30* have been tested using the developmental neurotoxicology protocol.[8;25] For the rest, the painful truth is that we are flying blind. For combined exposures, even if we were to study *only* these top 3,000 chemicals in combinations of *only* three we would need to perform *85 billion tests,* which is basically impossible.

Recent science is teaching us much about the complexities of the ways that chemicals may act: differently in low than in high doses; differently in embryos and juveniles than in adults; differently in males than in females; and differently in relation to everyone's genetic individuality. In fact, genetic vulnerability to exposures can vary between individuals as much as 100- to 1,000-fold, or even more. As this new science advances, more and more scientists are realizing that our current screening tests for chemicals are not able to detect many newly appreciated classes of harmful effects.[24]

Finally, deciding how to assess exposures is a huge political battleground given the high economic stakes riding on the outcomes. This problem has received a lot of recent press in relation to the pharmaceutical industry but it is true of other industries as well. The politics of science and between scientists can greatly prolong the amount of time it takes to achieve consensus on updates in regulation, screening and scientific guidelines that might allow catch-up with new scientific research. Meanwhile, the marketplace is governed by outdated standards.

Autism, Genes, Environment and Medical Problems in Autism

Both genes and environmental exposures should not be expected to confine their effects to any one system in the body. Virtually all of the cells in our bodies have the same genome and many of the body's core biochemical processes (which are shaped by genes) occur in many or all of our bodily systems. Therefore, a genetic change may express itself in many bodily systems and an environmental exposure may target a biochemical vulnerability that is widely distributed in the body. The separation of the brain from the body is really an artificial distinction. All of our bodily systems are interconnected.

Some bodily systems more directly interface with the environment, such as the gastrointestinal system, which is the first port of entry of many environmental exposures, and the immune system, which deals with responses to outside intrusions into the body. From the perspective of gene-environment interactions, it should come as no surprise that we are seeing gastrointestinal and immune problems in many autistic individuals.

Autism as a Whole-Body Condition

It may well be that the medical problems in autism are not incidental or extra problems "on top of" the autism but rather core parts of the problem. They may well be manifestations of systemic biological disruptions that lead, at the level of brain output, to behaviors that meet criteria for "autism," and also, at the same time, lead to various kinds of bodily illness—digestive system problems, allergies, sleep disruptions, seizures, sensory disturbances, low muscle tone, clumsiness and a variety of other problems that in various combinations affect many people with autism.

When people think about autism, they often think of the brain problems as primary and call it a "neurobiological" disorder. No doubt the brain is involved in producing atypical behaviors. However, from the perspective of gene-environment

interactions, we need to ask whether the brain is the primary target, or whether the brain could be affected at the same time as—"in parallel" with—or even "downstream" of, other bodily changes, such as in the immune system. Perhaps the brain is "caught in the crossfire" of whole-body changes related to environmental stress.

Could Brain Changes in Autism Reflect Environmental Impacts?

Once we consider environmental impacts on autism, important questions are raised about how we interpret the changes we have seen so far in brains of people with autism. It is certainly true that researchers have documented brain differences in individuals with autism. One way of interpreting these changes is to presume they are genetically based, and therefore to look for correlations between genes, the regions of the brain that show changes, and the types of behaviors we see in autism. However, another way of thinking about brain changes in autism is to use the evidence as clues to help figure out what biological mechanisms are driving the problems.[12] Recently researchers have been documenting evidence of inflammation and oxidative stress in the brain.[21;26;27] These kinds of changes are well known to be two of the main ways that the body and brain respond to an overload of metabolic and environmental stressors. There are also other changes that have been documented in brains from people with autism that can increase the brain's "excitability" (i.e., intensity of response to stimuli).[22] Such changes can be caused by both genetic and environmental factors, which alone, or even more, in combination tip the system in the same "excitable" direction. There are also various possible ways that environmental impacts could be related to other brain changes researchers have documented, such as larger brain size and reduced brain coordination, as well as limbic system and cerebellar changes.[10;15] These brain changes and their impacts are hard to explain by a purely "genetic determination" model. A "gene-environment interaction" model works better. And since the brain—which after all is a wet organ of the body and not just an information-processing computer—may be "downstream" of other body changes, a brain-body interaction model may explain more changes than looking at the brain by itself.

The important thing to remember here is that we don't need to make an "either-or" choice between "gene and environment" or "brain and body;" instead, we need to take a "both-and" approach, and learn how the members of each pair work together.

Autism and the Environment: Can We Find the Cause?

We have sketched the overall picture that many dramatic changes are happening in our environment that may be contributing to the dramatic increases we are seeing in autism. Can we argue that among all of the environmental factors there is a single exposure, infectious agent or stressor that uniquely accounts for the rise of autism? So far, studies have not established strong support for this theory. At the same time, there may be some environmental exposures, such as heavy metals, that contribute more strongly than others. Getting answers to the question of cause is important for two main reasons. The first is that if we find out what is causing harm, we can work on preventing future harm. The second is that if we understand the mechanisms by which particular causes or triggers contribute to autism, we can work on targeted biomedical treatments that halt or even reverse the injuries.

Environment and Final Common Pathways

Realistically, it will probably be quite a while before we definitively establish cause, if we ever do. What are we to do right now about helping individuals in a whole-body way with their whole-body autism? How do we know where to start, given the likelihood of prolonged disagreement and debate about both body and environment in autism, as well as the huge number of poorly tested chemicals and other stressors and the essentially infinite number of combinations in which we can be exposed to them—plus variations in the timing of when we are exposed? In some respects our bodies make it a little easier for us, in that we only have a finite number of metabolic pathways through which we handle and eliminate environmental exposures and stress. This means that many different factors converge onto a smaller number of body systems, which are "final common pathways" for environmental responsiveness. From this vantage point, researching and treating the body's mechanisms for handling and eliminating environmental stressors is central to strategies for treating and preventing the impairments of autism.

Autism Recovery: Plausible in the Gene-environment Model

We are hearing a growing number of reports of children recovering substantially or completely from their autism. Recovery does not mean leaving behind the gifts and creativity that can accompany autism, but instead, leaving behind the physical suffering and narrowed options associated with impairments. Some of these recoveries are attributed to intensive behavioral therapy; some to intensive biomedical intervention; and many to a combination of both. Although autism has traditionally been considered incurable, the "incurability" is merely an assumption—it has never been scientifically proven.

From a gene-environment, whole-body approach, it makes sense to consider the possibility of recovery from autism to be

scientifically plausible. Environmental causes and triggers are not inevitable, and many of their effects may be reversible. In particular, environmental exposures can change brain function (for example, brain metabolism, coordination and signaling properties) and not just hard-wired brain structure. Treatments including stress reduction (e.g. from behavioral interventions) as well as biomedical treatments can improve aspects of brain function. In principle, this opens the possibility of improvement and successful treatment. As we learn more details of brain-body interactions in autism, we can expect a clearer picture of how we can improve brain function not only by treating brain and behavior, but also by treating body problems that impact the brain.

Currently efforts are underway to study autism recovery,[7;18] and to see whether we can find cases where claims of autism recovery can be rigorously documented by reliable testing before and after treatment. These efforts parallel those that were needed to rigorously document autistic regression before many people would believe that it could occur.[29] We can also study recovered children to answer some critical questions. We need to know whether there is something different about the children who improve or recover, or whether the recovered children were just lucky to receive the combination of treatments that worked for them. Either way, we need to know how to predict which treatments will be right for each child and to optimize treatment protocols.

Final Common Pathways and Autism Recovery

Many biomedical interventions in autism, particularly non-pharmacological and "non-traditional" approaches such as nutritional supplementation and elimination diets, have seemed paradoxical and peculiar from the vantage point of autism viewed as a genetically determined brain disorder. However, when we examine these approaches from the gene-environment, whole-body model's perspective, we see that they are designed to target the body's "final common pathways" of response to environmental exposures and stressors.

Two common non-drug biomedical interventions are nutritional supplementation (adding what is insufficient)[1] and elimination diets (removing what is irritating). Nutrients are co-factors that, among many other things, assist in the body's biochemistry of detoxification. Many nutrients are depleted in a diet of industrially-produced processed foods as well as poorly absorbed in the presence of gastrointestinal disturbances. This leads to nutritional insufficiencies that occur at the same time as exposure to toxins and other stressors increase the body's need for these very nutrients. Moreover, explosively burgeoning research in the field of nutrigenomics is uncovering reasons for huge differences in nutritional needs between individuals,[17] meaning that some people will be more sensitive to nutrient depletion than others, and some individuals will require greater quantities of nutrients than others to meet either their basic needs or even more, their nutrient needs under stress.[2] Elimination diets attempt to remove stressors that irritate and inflame an already struggling immune system.[16] Both of these interventions (and others as well) are aimed at improving the body-brain's resilience—its ability to function, regulate itself, and handle environmental and emotional stressors.

Not all of these biomedical approaches work for every individual with autism. Part of the problem in applying and evaluating biomedical treatments is that children can arrive at autism through many different underlying biological routes, leading to the need for a range of different treatment approaches. If treatments are evaluated on a group of autistic children who have different underlying biological causes and mechanisms, then evidence that approaches are successful for some sub-groups will be washed out by averaging these good responses with poor responses in children whose biology is different. Another challenge is that many autistic children appear to have a lot of interacting metabolic disturbances, making the treatment of one problem at a time less effective than treatments for several facets of the condition that are given in combination. This is a problem for clinical research, where clinical trials usually involve studying one treatment at a time. Effective research on these autism treatments, like effective research in many other domains where our appreciation of complexity is growing (e.g. genomics, metabolomics, nutrigenomics), will require innovation in study design methods.

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Autism as a Case Study of Environmental Illness and Treatment

It has been proposed that autism has features in common with other neurological diseases such as Alzheimer's and Parkinson's disease (particularly the environmental responsiveness and brain inflammation that all three conditions appear to share)

and with other illnesses with strong environmental components such as various immune and autoimmune diseases. The idea that different disease diagnoses that occur at different points in the lifespan may share some common underlying mechanisms is gaining more support.[3] This means that more work needs to be done not just on the behavioral overlaps between autism and other neuropsychiatric disorders (e.g. obsessive-compulsive disorder, language impairment), but also on the physiological overlaps (e.g. metabolism, biochemistry, immune system, exposure history) between autism and other disorders. This is relevant to developing treatments. For example, the drugs memantine (approved for treatment of the symptoms of Alzheimer's disease related to brain excitability), minocycline (used in Alzheimer's, Huntington's Disease and Parkinson's disease to reduce brain inflammation) and pioglitazone (approved for diabetes and associated with reducing immune activation) are now in clinical trials for autism treatment. Treatments that target symptoms or underlying functional problems may be helpful for more than one condition. Thus, advances in research and treatment in autism may both help and benefit from advances in research and treatment of other conditions. And all of these environmentally modulated illnesses will benefit from making our environment safer and healthier.

Autism as a Wake-up Call

The rise in autism diagnoses, along with the rise in other immune and chronic illnesses, is really a wake-up call. Put alongside the warnings about the ecological instability of our planet, it shows that our situation is serious. It calls for pulling out all the stops and throwing our best intelligence, resources and organization into *getting a grip*. Autistic individuals may not be "different" from the rest of us but simply "more sensitive" to environmental injury—they may be the "canaries in the coal mine" warning us of impending greater disaster. If the level of environmental insults continues to rise, more children and more adults—and more of life on earth—will experience harm.

Toward Regrouping our Priorities and Getting a Grip

Being touched by autism is a life-transforming experience. It makes huge demands on our time, and it forces us to think "outside the box" and across boundaries in order to rise to its challenges. It requires partnerships of many kinds—doctors with parents, scientists with clinicians and patients, parents with their autism spectrum children, schools with health care providers, governments with communities, and more—all of which call for ongoing creativity. It also requires a willingness to face painful realities about the limits to our knowledge and resources, and about many mistakes we did not know we were making. Dealing with autism on an everyday basis forces us to act on our best *judgment* even when critical areas of precise knowledge are lacking.

All of this is true as well of what we are facing and will increasingly face regarding the deterioration of our environment. Environmental deterioration will affect the health of a growing portion of the population and the earth's living and physical systems. It will be life-changing in profoundly inconvenient, time-consuming and disturbing ways. It is hugely complex and so will probably forever defy our efforts to define it with final precision. We can learn many things from our struggle to improve the health and functioning of autistic individuals that will empower us in facing other health and environmental challenges as well. We already have enough evidence to make the judgments that environmental factors are critical issues for autism. It is in all of our best interests to come to grips with these challenges now.

> "Autistic individuals may not be 'different' from the rest of us but simply 'more sensitive' to environmental injury..."

Autism may well be one of many forms of "collateral damage" from our uncritical trust in "progress," and in particular our unawareness of the many cascading "side" effects of our clever inventions (or, more accurately, "other" effects than those we intended with our narrow and short-sighted "cause-effect" models). This kind of damage challenges us to intelligently regroup our priorities without delay, and to learn the skills of keeping in mind complexity and interconnection. If we make an earnest effort now, perhaps we can avert irreversible stress on our health and our environment, and move instead toward more humane, sustainable ways of living that promote not harm, but the health and fulfillment for which we all yearn.

Turning our priorities now toward predicting risk, preventing harm and reversing injury in autism and in other environmental illnesses, and pursuing these policies in the setting of the broadest and most forthright awareness of the magnitude of the difficulties we face, will provide us with a positive focus that can bring us together in this time of great challenge and danger.

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