Autism: From Static Genetic Brain Defect to Dynamic Gene-Environment Modulated Pathophysiology

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Beyond Autism

Can genes determine which fifty-year-old will succumb to Alzheimer’s, which citizen will turn out on voting day, and which child will be marked for a life of crime? Yes, according to the Internet, a few scientific studies, and some in the biotechnology industry who should know better. Sheldon Krimsky and Jeremy Gruber gather a team of genetic experts to argue that treating genes as the holy grail of our physical being is a patently unscientific endeavor. *Genetic Explanations* urges us to replace our faith in genetic determinism with scientific knowledge about how DNA actually contributes to human development.

The concept of the gene has been steadily revised since Watson and Crick discovered the structure of the DNA molecule in 1953. No longer viewed by scientists as the cell’s fixed set of master molecules, genes and DNA are seen as a dynamic script that is ad-libbed at each stage of development. Rather than an autonomous predictor of disease, the DNA we inherit interacts continuously with the environment and functions differently as we age. What our parents hand down to us is just the beginning. Emphasizing relatively new understandings of genetic plasticity and epigenetic inheritance, the authors put into a broad developmental context the role genes are known to play in disease, behavior, evolution, and cognition.

Rather than dismissing genetic reductionism out of hand, Krimsky and Gruber ask why it persists despite opposing scientific evidence, how it influences attitudes about human behavior, and how it figures in the politics of research funding.

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Autism Status Quo: Genes, Brain, Behavior, and Hopelessness

To put the myth of genetic reductionism bluntly: DNA makes the rules; everything else obeys. It follows, then, that a complete understanding of living systems will ultimately be achieved—in fact, can only be achieved—by completing our genetic understanding.

Autism would appear to be a good, although disheartening, example. Autism has been considered to be a genetically hardwired neurodevelopmental disorder and is defined in the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders by a set of behavioral dysfunctions: impaired social interaction, impaired communication, and restricted and repetitive behavior. In plain terms, autistic people tend not to “get” how to interact with other people, are not good at figuring out what someone else is thinking or feeling, have all sorts of problems saying what they mean or understanding what another person means, and often do weird things like stacking up all the cans in the house over and over and having meltdowns when someone interrupts them. In fact, these behaviors occur in different combinations, proportions, and degrees, so that autism is now thought of as a “spectrum” of disorders.

This description, though standard, does not begin to convey how bad autism can be for some people and their families. Nor does it convey either the brilliance of many people with autism, even if they cannot talk, or the multisystem pathophysiology (prominently immune, gastrointestinal, and metabolic/mitochondrial dysfunctions) present in large numbers of persons with with autism.
Early on, autism was attributed to faulty parenting, but for some decades now the blame has been placed on genes and brain defects. The evidence to support this has been inferential but has seemed compelling. Twin studies indicated that identical twins are far more likely both to have autism than fraternal twins, which seems clearly to indicate that autism is the result of defects in a fetus’s genes. Changes in the brain have been identified that have been considered “defects” and attributed to prenatal genetic causes, although the specific genes and mechanisms by which these changes could be created have not been delineated or, if they have been delineated, have applied to only a tiny minority of individuals with autism. Overall the belief has been that broken genes cause the autistic child to be born with a defective brain that, in turn, produces a lifetime of dysfunctional behavior. It makes sense: broken genes, broken brain, broken behavior—a life sentence, hopeless. Like a chromosome-abnormality-based condition such as Down syndrome, it is all set in stone before you are even born, and you are stuck with it.

That has been the theory, and that is certainly the way it can look when one is facing autism head-on. In a typical case, a 4-year-old boy named Jeff was diagnosed with autism. The doctor explained to his parents that there was no way to undo the damage that Jeff’s brain had been born with, any more than one could turn the limbs of a Thalidomide baby into normally developed arms and legs. “At some point,” the doctor warned them, “you’ll need to put your boy in an institution. You simply won’t be able to take care of him.” He then handed them a brochure for an institution where he had already put Jeff on the waiting list.

Jeff’s parents were shocked and, for a while, defiant. But eventually they came to the heartbreaking conclusion that the doctor had been right. Jeff was impossible. He constantly banged himself against the walls. He never slept through a night—and neither could his parents. He would spend hours fiddling with a plastic dish, just spinning it in noisy circles with an uncanny and irritating precision. For a while before his regression into autism he had at least been able to talk, but he lost that ability, and it never came back. Nothing ever got better. As Jeff’s mother put it, “Jeff was screwed for life and so were we.”

What is to be done? If it all begins with the genes, it seems clear that researchers need to find the genes that cause autism. It might then be possible to devise extremely precise molecular or genetic interventions that would undo the damage or at least provide a work-around. But after decades and many millions of dollars devoted to looking for the fundamental genetic explanation of autism, there has been no home
run. Instead, things have gotten more complicated. Genetic testing has become much more sophisticated, and more (actually many more) candidate genes have been identified, but there has been little progress in therapeutics, and it remains to be seen how useful gene and molecular targeting of therapeutics will be in improving the level of function and quality of life of those with autism.

Anomalies Undermining the Genes-Brain-Behavior Model

Although genetics has increased in complexity, observations have been accumulating that autism involves an array of phenomena outside the genes-brain-behavior model.

Not a Static Prevalence. The incidence of autism by some accounts seems to have gone up tenfold or more since 1985. Such things do happen when diseases become better known to the medical profession and to the public, but in this case the leap in incidence seems too high to be entirely due to a change in reporting. If autism is a genetic defect, why would it suddenly start occurring much more frequently and then keep doing so for twenty or more years? That is not how a genetic illness should behave. In spite of these numbers, a good, though finally diminishing, number of researchers do not believe that the increases are happening at all. Their refusal may have elements of circular reasoning: they attribute the statistical finds to the fact that autism has become much more widely known and is therefore much more commonly diagnosed than it ever had been, and they dismiss any possibility that there could be a real increase, on the apparent assumption that such an increase is impossible in a genetic disorder. But although many studies have shown that portions of the increase can be attributed to other things such as earlier age at diagnosis, changes in diagnostic criteria, or diagnostic substitution (i.e., labeling people autistic who previously would have been diagnosed with something else, such as mental retardation, attention-deficit/hyperactivity disorder, or epilepsy), no one has actually proved that the entire higher incidence is merely a reporting artifact and not at least in part a genuine increase.

In the past few years careful data reviews (including a review of every single reported case in California for an extended period) have parsed out cases that can be attributed to such other causes; they find that although a modest proportion can be attributed to diagnostic substitution, earlier diagnosis, and altered diagnostic criteria, from 40 to about 65 percent of the increase in numbers is an unexplained increase and could
very well reflect environmental influences.\textsuperscript{3} At this point one of the strongest arguments of those who claim that there is no increase appears to be that the science showing increases is not definitive.\textsuperscript{4} The word “environment” is even starting to crop up more frequently in essays of geneticists. So the reported increase poses a public health challenge that, given the seriousness of the affliction, certainly deserves serious attention. Studying environmental influences is at long last being named as a fundable research priority.

\textit{Not Just Genes: Environmental Contributors.} By now a growing list of environmental agents are implicated in increasing the risk of autism. There is evidence that proximity to pesticide application during pregnancy, proximity to freeways and other sources of air pollution, heavy-metal exposure, and maternal infections all contribute to increased risk.\textsuperscript{5} A long list of further exposures is under consideration, including substances that can cause harm by their presence (e.g., flame retardants) or by their absence or deficiency (e.g., essential fatty acids [omega-3 fatty acids], which are pervasively low in the population, or vitamin D, commonly deficient, which is important to immune and endocrine function, as well as to DNA repair mechanisms, and is potentially pertinent to the \textit{de novo} mutations being found in autism and now in other conditions as well).\textsuperscript{6}

\textit{Not Just a Few High-Impact Genes: Hundreds of Mostly Lower-Impact Genes.} Instead of finding a few genes, scientists have identified hundreds with possible influence. Even the small number of autistic children with identifiable genetic conditions include hundreds of different mutations, and the commonalities across these different genes that would produce autism are not yet clearly specified.\textsuperscript{7} Meanwhile, the yield of academic investigations into autism genetics has been more thorough testing methods but very little therapeutics. Some drugs seem promising, but to date drugs with any demonstrated efficacy have only suppressed symptoms like aggression and have not improved core behavioral features of autism.

\textit{Not Just Inherited Genes: De Novo Mutations.} Copy number variations (CNVs), which are alterations of the DNA of a genome that result in the cell having an abnormal number of copies of one or more sections of the DNA, have been found in autism, sometimes at a higher rate than in individuals without autism. A portion of these genetic changes are \textit{de novo} variants not found in the parents of the affected individuals.\textsuperscript{8}
Not Even Mainly Genes: Substantial Environmental Contribution. For years twin studies have been cited to prove the high heritability of autism. Concordance (shared diagnosis) figures of 90 percent of identical twins and 10 percent of fraternal twins were used to justify an intensive focus on genetics to the exclusion of environmental influence. In the largest twin study to date, lower monozygotic (identical twin) concordance and higher dizygotic (fraternal twin) concordance yielded a smaller gap between autism rates in identical as compared with fraternal twins, with 55 percent of the variance for strict autism and 58 percent for autism spectrum explained by shared environmental factors, with moderate genetic heritability of 37 to 38 percent. The article’s conclusion suggesting a greater role for environmental factors and a smaller role for genetics than heretofore presumed was hailed by some as a game changer, although its methodology infuriated many genetic researchers.

Not Just Brain Genes. For years geneticists looked only for “brain genes” in candidate regions of the chromosomes, but they may have been overly limiting themselves. Dan Campbell of Vanderbilt University, along with Pat Levitt, a neuroscientist now at the University of Southern California, identified the MET gene as significant in many people with autism and found that its impacts ranged from the brain to the immune system to the gut and beyond and that it was environmentally sensitive.

Not Just Local, Modular Brain Disturbances: Whole-Brain Involvement. One of the most replicated findings in the brains of individuals with autism has no immediately obvious relationship to the core defining behaviors of autism. Autism brain research had hunted, not very fruitfully, for specific brain areas that might explain the “aberrant behaviors” of autism, but the field was surprised by an increasingly replicated finding of larger brains, identified by postmortem brain weight, head circumference, and MRI measures. My MRI brain-volume analyses, as well as those of others, revealed that the extra brain volume was distributed throughout the brain rather than being centered in the regions of the brain known to be associated with the language and behavior capabilities affected by autism.

Not Just Prenatal. Researchers have found that autistic children are not simply born with enlarged brains; they develop this enlargement postnataally. This contradicts the previous orthodoxy that autism is caused by alterations to brain development in utero. There is a massive growth spurt for the first two years after birth, with some parts of the brain (like
prefrontal and cerebellar white matter) being as much as a third bigger in some children with autism.\textsuperscript{14} This is a huge size difference in an organ that is tightly spatially confined by the skull. Then the growth rate slows down, and by adolescence the brains of people with autism are, on average, slightly smaller than normal. In retrospect, the long and strongly held belief that autism was based on prenatal brain changes was supported only by a modest number of observations in postmortem tissue samples of older individuals. The interpretation that these cellular changes could have occurred only prenatally, and the grip it held on the field for so long, went far beyond what the data could truly support. Alternative explanations of observed cellular changes have been emerging that rest on postnatal (and often toxic) influences, as I will discuss later.

\textit{Not Necessarily Present at Birth.} Autism was initially assumed to be present from birth. Parents’ reports that their child “regressed” were dismissed as a function of the parents not knowing much about child development. However, regression is now an established phenomenon that occurs in many, though not all, children with autism, although it may occur differently—rapidly or gradually—in different children. Videotapes of children before their regression were rigorously analyzed, and the complete or near-complete absence of abnormalities before regression was verified in a number of cases.\textsuperscript{15} Although it can be argued that regression is just the late expression of inborn genetic tendencies, it is also possible that postnatal influences may have contributed to the regression; this cannot be excluded a priori.

\textit{Not Just Behavior.} In addition to the behaviors at the core of the psychiatric definition of autism, a plethora of other neurological problems are very common. These include seizures (present in 7 to 46 percent), brain epileptiform activity (present in possibly the large majority), significant sensory threshold and sensory integration problems, coordination and gait problems, oral motor dyspraxia impacting swallowing and speech, dyspraxia associated with other activities such as hand use, disturbed sleep, major alterations in speech prosody, and in some cases catatonia. These phenomena suggest underlying alterations in the brain’s substrate that go substantially beyond the behavioral problems that are most obvious to our social intelligence.

\textit{Not Just the Brain.} Many people with autism have chronic somatic medical problems that are not included in autism’s definition.\textsuperscript{16} It has been widely observed clinically that autistic people suffer more than their
share of gastrointestinal disorders, including intractable diarrhea, severe constipation, gastroesophageal reflux and esophageal ulceration, and deficient pancreatic production of digestive enzymes. There are also problems that interface between the gastrointestinal system and behavior, such as lack of toilet training and extreme “picky eater” behavior—narrow, nutritionally inadequate eating preferences (generally beige-colored foods like wheat and dairy) with food refusal. This has variously been assessed as being coincidental, not coincidental, and vanishingly unlikely to be coincidental. Some of these disorders are quite painful or interfere in other ways with normal life, such as the painful gastroesophageal reflux and esophagitis that can disrupt sleep and lead to self-injurious behavior, particularly in nonverbal individuals who cannot use words to get help for their pain (although even highly verbal individuals with autism may have serious problems locating the specific source of pain, presumably because of sensory processing issues). An array of immune problems (allergies, recurrent infections, autoimmunity, and mothers with autoimmunity) are common as well. Yet until recently discussion of these nonbehavioral concerns was frowned on, and the corpus of research on these issues is only beginning to develop in earnest.

Not Just Deficit: Giftedness and High Intelligence. Although the assumption that autism is predominantly associated with mental retardation has been taken as a verity, it is now being called into question. First, the quality of the studies that claimed to ascertain this has been criticized. Second, it appears that IQ tests relying on verbal instructions underestimate IQ—in one study the Wechsler scales of intelligence scored predominantly in the mental retardation range, whereas the Raven’s Progressive Matrices (a strong measure of fluid intelligence) did not. Many people with autism in fact demonstrate great creative skills and brilliance even when they cannot talk. Increasing use of augmentative communication devices, on the order of a social movement within the autism community, is yielding unexpectedly articulate communication from a growing number of nonverbal autistic individuals. The obstacle with speech may well be dyspraxia (impaired ability to initiate or coordinate verbal production) rather than a deficit of language capacity itself. All of this raises questions about the pertinence of the many genetic studies that hunt for genes associated with mental retardation in their study of autism. In addition, the behavioral meltdowns of nonverbal individuals can sometimes be due to sheer boredom and frustration with a primitive, repetitive curriculum far below their capabilities. In her memoir Strange Son, Portia Iversen relates that when her 9-year-old nonverbal son was given an assistive communication device, it was discovered that he could
read and understand English and Hebrew and could do fourth-grade math, all without having received explicit instruction. Others in similar positions can handle math or physics or write poetry.

Not a Life Sentence: Evidence of Remission and Recovery. The idea that autism is a static encephalopathy is being challenged by evidence that autism can remit. Some autistic children, for example, get a lot better when they have a fever. They may make eye contact or even talk, which they had not been doing otherwise. This has been reported in significant numbers of autistic individuals, although the mechanisms underlying this phenomenon are still under investigation; hypotheses range from immune modulation to bioenergetic upregulation to altered neurotransmitter activity. One mother told me that she was glad whenever her young son had a fever because he would become more communicative and, as she eloquently put it, she would “get to visit with her son.” Even if such spontaneous remission is transient, it would be unsurprising behavior for a disease but is hard to explain for a condition arising from a brain whose incapacity is assumed to be permanent and unalterable.

Beyond transient remission, there are also growing numbers of cases where substantial improvement in condition or even loss of autism diagnosis has been documented, usually after intensive treatment. A small but growing body of literature is addressing what this means for how we think about autism. The National Institute of Mental Health is carrying out an autism remission study in which it is identifying such cases and doing exhaustive history and testing (neuropsychological studies, genetic studies, immune measures, brain studies, and others) to learn what may be different about these children as compared with those who do not remit or recover.

In summary, evidence is shifting the conception of autism from a genetically determined, static, lifelong brain encephalopathy to a multiply determined dynamic systems disturbance with chronic impacts on both brain and body.

Dynamic Physiological Processes Implicated in Autism. The problems in the body beyond the brain have been a particularly challenging dimension to incorporate into the world of autism, in part because of the depth of the belief that autism is a brain or neurological disorder. The modular
division of the body into distinct organ systems, each with its own textbook chapter, has difficulty linking body and brain. With the rise of systems biology, the pathways back and forth between brain and body are becoming elucidated in detail; they supersede the belief that the brain is protected from the body by a more or less impermeable blood-brain barrier and that the brain is immune privileged—that is, shielded from systemic immune problems.

A further barrier to considering the body’s impact on the brain was the reaction to the work of Wakefield, who argued not only that there was a link between autism and vaccines but also that this link was mediated through the gastrointestinal system. For the better part of a decade any attempt to discuss gastrointestinal or immune issues with autism was construed as a support of Wakefield’s vaccine hypothesis, and it was difficult to discuss, let alone get funding for, clinical or research observations about these problems. One way around the essentially taboo character of somatic problems in autism was to treat them as coincidental symptoms. For example, one could talk about gut problems provided one made it clear that they did not cause the autism in the brain. Improvement after treatment of gut problems, which is often observed, would then be explained as a consequence of reduction of pain and discomfort, but not of any direct impact on core brain mechanisms generating autistic behaviors.

Systems biology is increasingly documenting phenomena that blur the boundaries across organ systems. It is becoming commonplace to discuss the impacts on the brain of immune cytokines, gut microbiota, nutrition, and stress. This is helping dissolve the taboo in autism about considering body-brain relationships. Along with this more general shift in scientific framework, more specific documentation of disturbed systems biology in autism has accumulated. The following are some of the dimensions of this:

**Immune Dysregulation.** Hundreds of articles have documented immune abnormalities in autism, although not all have been of high quality. Abnormalities include alterations in immune cytokines, presence of autoantibodies including antibrain antibodies, inflammation, and more. In 2005 Pardo and colleagues at Johns Hopkins University published evidence of innate immune activation in brain tissue. In particular, they identified activated glial cells—astrocytes (or astroglia) and microglial cells, visible microscopically with special staining techniques but not macroscopically via brain imaging. Although the findings of this study electrified some segments of the autism world, they were shunned by others. More recently a number of other groups have replicated these neuropathological findings, and several studies of gene expression in brain tissue have supported the existence of this phenomenon as well.
Mitochondrial Dysfunction. A role for mitochondria is being identified in a plethora of chronic diseases ranging from cancer and obesity to diabetes and neurodegenerative diseases. A higher rate of clear mitochondrial disorder in autism (about 5 percent) than in the general population and biochemical evidence of milder mitochondrial dysfunction in as many as one in three persons with autism have been identified in articles and meta-analyses. The idea of mitochondrial dysfunction in autism has met with some consternation and avoidance, again to a significant degree because of the link to the vaccine controversy. In this case the link is particularly driven by the daughter of a neurologist in training at Johns Hopkins who developed autism after receiving nine vaccinations in one day; her family received a settlement from the U.S. Court of Federal Claims, which hears vaccine injury lawsuits. Officials argued that this was a rare occurrence, given that this child had a genetic vulnerability to mitochondrial disorder that was just triggered by the vaccines and would have happened soon enough anyway. More broadly troubling is the well-known exquisite vulnerability of mitochondria to a wide range of environmental insults. The existence of debate about mitochondrial disorder versus dysfunction seems much more marked within the autism community than in other conditions where thousands of articles have been published about the occurrence of mitochondrial dysfunction even in the absence of established genetic causes of mitochondrial disorder.

Oxidative Stress. Oxidative stress is also being identified in many chronic illnesses. Free radicals are normally produced in small amounts by oxygen metabolism. These free radicals can damage DNA, molecules, cell membranes, and other structures, but under normal circumstances they are “quenched” by antioxidants. When the production of free radicals exceeds the body’s antibiotic reserves, there is a buildup of oxidative stress. Various laboratory indicators of oxidative stress, as well as genetic vulnerabilities to this problem, have been identified in individuals with autism and also sometimes in their mothers.

Methylation Disturbances. Disturbances of methylation have been identified in people with autism. These disturbances potentially affect DNA methylation and hence epigenetics. They also affect other processes, such as neurotransmitter synthesis, cell membrane function, and silencing of viral genes. Associated with these disturbances are abnormalities in sulfur metabolism, which can affect the production of antioxidants and the elimination of toxicants.
Disturbed Gut Microbial Ecology. Data supporting disturbance of intestinal microbial ecology in autism have been accumulating. These include direct measurement (e.g., abnormal variants of Clostridia, presence of Desulfovibrio that can alter sulfur metabolism) and indirect evidence (such as animal models of autism-like behavior and brain changes with exposure to by-products of gut microbial metabolism).35

Hormonal Dysregulation. Indications of possible hormonal dysregulation include atypical growth patterns, abnormal patterns of autonomic arousal (both hypo- and hyperarousal), marked changes at puberty (e.g., sometimes seen are increases in aggression and severe premenstrual syndrome), sleep disturbances, hypothyroid, and seizures.

Active Pathophysiology, Genes, and Environment

All of these phenomena are not simply systems disturbances; they are active physiological processes, shifts in ongoing functional activities in the organism, that are by no means necessarily caused by genetics and are by no means necessarily related to hardwired brain changes. Immune problems are clearly not all genetic because the immune system mediates between organism and environment. Oxidative stress and mitochondrial dysfunction are known to be promoted by myriad environmental exposures. Genetic vulnerabilities to these problems are common in the general population, but when several occur in one individual, the likelihood of being autistic can increase greatly (in some cases manyfold). Even so, given the increased vulnerability to environmental impact conferred by these gene variants, the outcome of autism might be not so much caused as facilitated by such genes, with the degree of environmental exposure determining much of the risk and the severity of the outcome.

Active Pathophysiology and the Brain. Genetic research has focused on the synapse as the central locus of brain disturbance in autism spectrum disorders and has looked for synapse-impacting gene variants that might be at the root of autism. This fits the idea that genes, which are inborn, change the brain in a way that inevitably causes autism.

However, the active, dynamic pathophysiological processes listed above may expand that narrative: (1) they can affect the mechanisms and milieu of synaptic functioning, and (2) they have many triggers, not only genetic but also environmental, and so are not necessarily inborn and unalterable.
Impact on Synaptic Functioning. Immune disturbances are known to affect neuronal excitability, and pro-inflammatory cytokines can increase vulnerability to seizures, which are evidence of major synaptic dysfunction. Mitochondrial dysfunction can be a consequence or a cause of seizures and may also alter the function of neurons and neuronal systems in more subtle ways. Gut microbial by-products can have pharmacological and immunological impacts on the brain as well.

Given these considerations, it can be argued that genes do not uniquely compromise synapses, but that environmental factors and their physiological consequences can also impact the molecular regulation of synapses and networks. But how important is that impact?

Could Active Pathophysiology Be Impairing Connectivity?

One of the core abnormalities in autism brain function appears to be altered, and usually decreased, connectivity and coordination among areas of the brain. By now there is a large literature that supports this. The neurocognitive functions considered to be core features of autism involve complex information processing. Thus it would make sense that impairment in connectivity and coordination would lead to less nuanced function in these areas of complex processing.

From the point of view of the gene-brain-behavior model, showing the association of a gene variant with an alteration in connectivity would seem to imply that this gene variant causes the connectivity issue and therefore causes autism. This would generally seem to imply that connectivity abnormalities, being genetic, are static, lifelong features of brain function in affected individuals.

However, a recent article by Narayanan and colleagues showed that brain connectivity could be increased in a matter of minutes after administering propranolol, a drug that reduces sympathetic nervous system activity (the “fight-or-flight” or stress part of the autonomic nervous system). They theorized that sympathetic activity increases “noise” in the “signal-to-noise” ratio of the brain, and that reducing this noise allowed the brain to have greater signal—greater bandwidth for accessing more remote parts of its networks. This finding opens the door to other types of nongenetic mediation of brain connectivity. In particular, brain excitotoxicity, a consequence or concomitant of many of the above-listed pathophysiological disturbances, may alter neuronal function and lead to altered network function.

Clinical phenomenology of ups and downs in some people with autism also suggests that the functional status of brain networks may be
variable. In addition to transient improvements with fever, there may be
marked improvements on a clear-fluids-only diet before medical pro-
cedures; moments of verbal lucidity in nonverbal individuals under condi-
tions of emotional intensity; and striking though transient improvements
in individuals receiving steroids for other reasons (e.g., asthma attacks)
or other immune-modulating drugs or upon emerging from anesthesia.
Children and adults under these circumstances may suddenly be socially
interactive when they were previously remote, verbal when they were
previously nonverbal, or spontaneously articulate when they were previ-
ously only repeating stock phrases. Conversely, some people with autism
also show marked deteriorations with exposures to allergens, certain
foods (e.g., gluten and dairy, or what some parents have called “pizza
psychosis”), or various environmental agents. Thus the association of
variability in function with environmental stimuli supports at least a de-
gree of environmental modulation of brain function.

Does Active Pathophysiology Modulate Genetic Substrate, or
Could It Be a Primary Cause of Brain Dysfunction?

If you believe the narrative that genes cause connectivity disturbances,
then environmental modulation of synapses and networks can only be
decoration on the cake, not the cake itself. On this view connectivity
problems are inborn.

But how does a narrative implying inborn dysfunction explain autistic
regression? How do toddlers who previously seemed normal become
transformed into being autistic? Was the connectivity problem always
there? If so, why did it turn into autism at a certain point? And if the con-
nectivity problem was not always there, what happened to produce it?
There are actually almost no pertinent brain data during the period before
the diagnosis of autism when the brain events creating autism would pre-
sumably occur. On the basis largely of data from older individuals, there
are an anatomical theory and a functional theory for how connectivity
problems develop.

The anatomical theory is that there is early brain cellular overgrowth
that alters the cellular substrate of networks, with hyperactive short-
range and hypoactive long-range connections.\textsuperscript{43} This overgrowth is as-
sumed to be genetically driven. This model generally predicts increased
cellular density. But brain-imaging data are contradictory on this point.\textsuperscript{44}
There are many reports of larger brain volumes, but measuring volumes
alone does not tell anything about the cells or other substances that may
be contributing to the volume. Other forms of brain imaging can look at
tissue characteristics, and these imaging techniques have yielded data that do not necessarily support the assumption that “bigger” equates with “more cells.” Brain imaging of metabolites (magnetic resonance spectroscopy) generally shows lower metabolite density—and, in particular, a reduction in the concentration of n-acetylaspartate, a marker of neuronal integrity or neuronal density. And brain imaging of white-matter integrity (diffusion tensor imaging) has sometimes shown that the white matter is less organized rather than more densely packed. These data suggest that the large brain and brain-region volumes need to be accounted for by something other than the presence of more cells.

The functional theory is that big brains come from ongoing cellular dysfunction. In particular, cellular dysfunction associated with inflammation and mitochondrial-bioenergetics-oxidative stress leads to cellular swelling as well as impaired cell fluid transport and increased extracellular fluid, and this set of cellular disturbances, rather than greater cell or fiber density, is what leads to bigger volumes. In this model the larger size is not due to a greater density of optimally functioning neurons and networks but instead to dysfunctional tissue changes such as fluid buildup or even “swelling.” These physiological problems may or may not require a substrate of genetic mutations to create vulnerability at the synapse. This theory is more consistent with the above-mentioned brain-imaging findings of lower density of metabolites and more poorly organized white matter.

The functional theory further posits that it is not so much the number of cells or fiber tracts that alters brain activity as the chemical milieu of the cells and synapses. The biochemical and immune environment at the cellular level can alter the communicative functions of neurons (and of glial cells, as I will discuss shortly). Particularly pertinent are excessive glutamate, an excitatory neurotransmitter, and the set of changes collectively known as “excitotoxicity.” These phenomena are known in other settings to contribute to brain excitation and seizures.

A 2003 article by Rubenstein and Merzenich positing that an increase in the excitation/inhibition (E/I) ratio is at the core of autism was the first prominent statement of aspects of this functional theory. Not coincidentally, this functionally oriented article was also the first forthright statement of the interactive roles of genes and environment and also of the multiple possible “combinatorial” pathways to this increased E/I ratio.

The idea here is that overly intense brain excitation could be a functional disturbance that has an environmental and active pathophysiological component, not just a genetic component. Documentation of brain
inflammation and immune activation in autism changed the playing field because it became clear that we were not dealing with healthy tissue that was wired differently but rather with brains that were having health problems with their cells. These health problems, as mentioned, particularly related to glial cells. Although these cells were previously characterized merely as helper cells or “nurse cells,” the critical nature of their functions is now being identified. Glial cells outnumber neurons in the brain approximately ten to one. Unlike neurons, they readily generate new cells. Whereas neurons are shielded (by glial cells) from direct contact with the blood-brain barrier, microglia initially enter the brain through that route, and astrocytes wrap the blood-brain barrier. In fact, microglia and astroglia mediate environmental impacts in the brain.

Astroglial cells not only support core metabolic features of neurons but also may even control the very formation of synapses. They also perform a variety of other functions, such as modulating glutamate and sequestering toxins and heavy metals (until they get overloaded). Beyond these metabolic functions they also participate in networks—they are linked together by gap junctions to form vast syncytial networks communicating via calcium waves—and they have their own “gliotransmitters.” Microglial cells are derived from monocytes, which are systemic immune cells, and they play an immune function in the brain.

Astroglia and microglia are activated by stressors such as infections and toxins. When they are activated, they perform immune and cleanup functions, but if the situation is not resolved, a chronic cascade of aberrant chemistry occurs, and they increase brain oxidative stress and excitotoxicity. Chronic activation of these cells is a major contributor to many neurodegenerative disorders.

From Genes and Neurons to Environment and Glial Cells

Just as fully understanding the causes of autism requires decentering from genes, fully understanding autism’s brain mechanisms requires decentering from neurons. The identification of immune-activated astrocytes and microglial cells and the upregulation of glial genes in autism brain tissue raises not only the commonly asked question of what is causing this but also the more rarely asked question of how these immune changes might affect how these cells perform their basic functions. What happens to the effects of these glial cells on synapses and networks when they are immune impacted? This question is not at all specific to autism. But in neurobiology (which some have suggested should be renamed “neurogliobiology”) it is not yet a well-developed research area.
Research is showing that glial cells can be critical contributors to severe brain derangements like seizures. Less well investigated is the contribution of glial pathophysiology to milder but still vexing features of brain dysfunction. In autism these features include sensory hypersensitivity, sensory integration problems, attention deficits, sleep disturbances, dyspraxia, and motor coordination abnormalities.

Cause?

Including glial cells in brain models of autism would allow further exploration of the mechanisms of postnatal emergence of autism (particularly regression) and of the ups and downs that are hard to explain in a purely neural model. But even more, if active pathophysiological processes, mediated by glial cells, are sufficient to alter synapses and brain networks, is it still always necessary to have an underlying genetic “cause” for autism? Or could someone with no special genetic vulnerability develop autism just from an environmental exposure or from the cumulative impact of a series of possibly diverse environmental exposures? At present this is a rhetorical question, but I think that the grounds for asking it are strong enough that research should be pursued to answer it.

Conversely, if genes are in fact not absolutely necessary, are they still sufficient on their own to cause autism? This probably depends on the gene. But there are issues even with genes of strong effect. Here we can look at genetic syndromes where there is a high incidence of autism, such as fragile X and tuberous sclerosis. These diseases certainly have high rates of autism, but the rates are by no means 100 percent. Only about 50 percent of individuals with fragile X have autism. What distinguishes them from the others with fragile X but without autism? At present this is not known. Could it be that these genes do not cause the autism but simply greatly increase the risk? Geneticists may assume that it is other genes that make some persons but not others cross the threshold into autism. Is it possible that those who do develop autism have it not only because of genes but also at least sometimes on account of an overlay of active pathophysiology? We do not know; we need to look. For this to happen, the genetic role in autism needs to be a question, not an assumption.

Smith-Lemli-Opitz syndrome (SLO) probably has the highest autism rates of any genetic syndrome. Cholesterol synthesis blockage is a key element of this syndrome’s impact, and when children with SLO are treated with cholesterol, their autism can go away. Furthermore, it is not unusual for children without SLO to have extremely low cholesterol (even below 100). Such children have been reported to have their cholesterol
go up as their autism difficulties reduce in response to other treatments, to improve in response to direct cholesterol administration, or both.\textsuperscript{56} This suggests some final common pathway to autism that can be arrived at by many routes. It also suggests that capabilities are obstructed but become accessible when the obstruction is removed.

Modulating Severity by Treating Intermediary Metabolism

Inborn errors of metabolism are a category of disease caused by known or presumed genetic problems. In some cases, such as phenylketonuria (PKU), public health programs in place (for PKU, newborn testing followed by a low-phenylalanine diet) can largely prevent symptoms even though a gene is involved. Modulation of autism severity by treatment in cases of documented metabolic disorder was reviewed by Page in 2000,\textsuperscript{57} and more examples have since been reported. Autistic symptoms associated with PKU are reduced by a low-phenylalanine diet,\textsuperscript{58} in hyperuricosuric autism by a low-purine diet with or without allopurinol,\textsuperscript{59} in patients with low cerebrospinal-fluid biopterin by biopterin supplementation,\textsuperscript{60} in some hypocalcuniuric autistic patients by calcium supplementation,\textsuperscript{61} in some patients with lactic acidemia by thiamine and/or ketogenic diet,\textsuperscript{62} in cerebral folate deficiency by folinic acid supplementation,\textsuperscript{63} and (as mentioned) in Smith-Lemli-Opitz syndrome by cholesterol treatments.\textsuperscript{64} Johnston offered a variety of mechanisms whereby metabolic disorders, sometimes with treatable aspects, might lead to neurological changes that could underpin autism.\textsuperscript{65} Zimmerman framed his report of promising immunological treatments in terms of a need for a search for reasons for their apparent efficacy, at least intermittently.\textsuperscript{66} James reported that her correction of oxidative stress and methylation abnormality profiles through intervention with methylcobalamin, folinic acid, and trimethylglycine was accompanied by qualitative clinical improvement,\textsuperscript{67} and work is proceeding to quantitate the observed qualitative behavioral improvements. Symptom severity was reduced in a trial of high-dose vitamin C in autism.\textsuperscript{68} In this regard but more generically, Ames and colleagues modeled high-dose vitamin therapy as a treatment approach for a range of genetic disorders characterized by decreased coenzyme binding affinity.\textsuperscript{69}

These examples suggest that in some cases one might find a metabolic key to remove or compensate for obstructions from pathways that are currently functioning poorly or not at all because of problems such as a high need for some metabolic substrate, excessive production of a metabolite whose breakdown pathway is slowed or blocked by a genetic defect, or impairment of energy production through some genetic defect.
slowing mitochondrial metabolism. The cases of cholesterol and of the large numbers of children with autism and biochemical indications of mitochondrial dysfunction but no detectable mitochondrial gene mutations also suggest that errors of metabolism may be produced by environmental rather than genetic factors.

Obstructed Rather than Defective

Given the clinical observations of transient improvement, persistent remission or recovery, and response to metabolic intervention, it becomes necessary to ask whether the brain in autism is truly and intrinsically “defective” or is instead “obstructed,” at least in many cases. These many clinical episodes indicate that the brain capacity is present, at least in many cases, but that there is a problem with organizing the means of expression, with organizing sensations into perceptions and constructs, or both. Autism from this point of view becomes more of an “encephalopathy”—an obstruction of brain function, possibly through an encephalopathy related to immune activation or metabolic dysfunction. If this is the case, research and care ought to be oriented much more to overcoming the encephalopathy so that people can express their full potential.

Note that I am not saying that people with autism should become “normal,” just more fulfilled. Members of the neurodiversity community might object that autism is an identity that should not be eradicated or cured. The discrepancy between that position and what I am saying may be a matter of terminology rather than of fundamental disagreement. Overcoming the systems-biology-based difficulties associated with autism may or may not eradicate the creative brilliance of many with autism. I would expect not, but this would remain to be seen—that is, it is an empirical question that needs to be answered by evidence, not just debate. But eradicating those gifts is not the intent here. Achieving full potential, however that may look, is the expected outcome of success in overcoming active pathophysiological problems.70

A point of commonality is that both the position I am presenting and the neurodiversity community object to common educational and therapeutic approaches that are palliative—controlling behaviors, warehousing, restraining, drugging. As I write, the 16-year-old son of a dear friend is being transferred to a regular high school. A year ago he was nonverbal and having seizures and had never talked to his parents. Now he still cannot talk, but he can type, and he has a lot to say about things over many of the years of his life—it turns out that he has been observing and understanding a great deal. Had he not had the nonstandard opportunity to develop typing ability, he and his family and others would never have been...
able to add communication with language to their relationships with him and his with them. And who knows what creative contributions he will make to the world as he goes forward?

Environment: The Gift That Keeps On Giving

Epidemiology is the field of investigation that most often comes to mind as the route to finding causes of autism. It is important for finding associations between environmental factors and changes in autism rates, but it does not explain how these environmental factors cause autism. Pathophysiology is where the rubber hits the road. Pathophysiology is the locus of how genes and/or the environment can cause autism. It takes environmental impact beyond looking for association between environmental agents and autism incidence and looks at how the environment affects underlying physiological mechanisms.

The environment has inched into the discourse on autism, small steps at a time. To date, the environment-autism discourse has largely mirrored the genes-autism discourse: just as genes were said to create a different brain-wiring diagram, so environmental agents could contribute to altered brain development as well. In both cases the deed is done right from the start, and as Jeff’s mother said, you are “screwed for life.” But why should environmental effects be confined to the early developmental period? Why should it just be about the brain? There is no a priori reason that they should be. And why should they necessarily be a life sentence? Environmentally vulnerable physiology can have impacts far beyond those constraints.71

Hardware or Software? No simple metaphor can truly map onto the complexities of molecular biology, but roughly speaking, the metaphor shared in these “early brain development” models of autism is that hardware comes before software. There is presumed to be some kind of fundamental alteration in architecture, be it of a cell receptor, a brain region, or a network diagram, and be it caused by gene, by environment, or by both together.

But with reflection on the role of active pathophysiological processes in altering synapses and networks, it starts to become conceivable that software, or so-called fluid processes, could conceivably precede architectural alterations. That is, the chronic persistence of biochemical, metabolic, immune, and signal-processing perturbations could skew developmental trajectories in micro- and macroanatomy. This shifts the central locus from genes to molecules and pathophysiology.
From Developmental to Early-Onset Chronic Pathophysiology. Once one takes this step, it is easy to take the next step and consider whether environmental influences might continue to modulate the severity of these software or fluid alterations in an ongoing fashion. That is, why could they not affect function—particularly but not exclusively brain function—even after the period when brain development can be perturbed? If this is so, then the distinction between “developmental disorder” and “chronic illness” starts to blur, and one starts to see an interacting dance between genes and environment that can begin from conception or even from preconception epigenetic influences.

From a Fixed Unitary Phenomenon to Modifiable Manifestations of Complex Interacting-Systems Problems

At this point the category of “autism” starts to deconstruct into a complex web of influences on brain and systemic biology, starting anywhere from before conception to after birth. Moreover, if dynamic pathophysiological processes can contribute through multiple pathways to significantly compromising ongoing brain function, and if this compromise is not necessarily permanent, then the very diagnostic category of “autism” may turn out to be a reification of a set of systemically interacting dynamic processes. That is, it turns a concept into a thing that is then treated as a unitary entity. This produces scientific and conceptual chaos.

Autism as an Epiphenomenon or Emergent Property of a Challenged System. But from a systems-biology vantage point autism stops being a unitary category and instead becomes an epiphenomenon—the behavioral output of a system where many things are conspiring to deplete the resilience and degrees of freedom of an increasingly vulnerable system. From a dynamic-systems point of view behavioral patterns are emergent properties of altered systems functioning—they are “patterns of behavior that ‘fall out’ of the structural and energetic status of the system without being represented in that system.” In the case of autism the structural and energetic status of the system is compromised. This leads the exquisite coordination of the brain to become, in some respects at least, less differentiated and less nuanced and to retreat to a less resource-needy mode of operation. It is as if the brain is conserving scarce resources. (This may also involve concentrating resources in certain areas where great creativity may emerge.)

If this is so, then giving the system more abundant resources (material, informational, or both) may allow the system to function more freely.
and flexibly. This underlying principle motivates a range of superficially different therapeutic strategies that seem to enable some with autism over time to lose their diagnoses. Resources may include supplying nutrient cofactors to overcome blocks in metabolic pathways, movement or communication support, biofeedback to learn stress reduction, communication support, and many other forms of medical, educational, behavioral, and neurophysiological intervention.

Specific Genetic Determinants or Final Common Pathways of Pathophysiology? Given the official DSM-IV definition of autism, many geneticists and others have believed that specific genetic determinants must exist to create such a replicable set of behaviors. More recently, though, with the identification of hundreds of genes, most of which are rare, that all contribute somehow to autism, it has become a challenge to find common themes across disparate influences. To address many disparate genetic mechanisms with a smaller number of evidence-based therapeutic approaches, one would need to identify a strategic node in some common network.

If one looks at the active pathophysiology contributors to autism, the picture is different. Many environmental contributors may cause or exacerbate inflammation, oxidative stress, or mitochondrial dysfunction, but it may not be necessary to identify precise molecular targets for treatments to have a major impact. The upstream environmental triggers of active pathophysiology—or its avoidance—can be influenced in fairly generic ways. Inflammation, oxidative stress, and mitochondrial dysfunction can all be significantly affected by diet, for example.

The idea that so-called autism is an epiphenomenon or an emergent property of a challenged system also extricates us from the constraints of needing to find specific determinants for specific behaviors, since from this vantage point the specificity of the behaviors does not arise from specific biological determinants but from the dynamics of the system.

Time to Get a Grip

If we look at biology through genetic lenses, then the terrain seems stable, and we have time to flesh out the mechanisms because they are not changing. But if we look at biology through dynamic lenses, where genes and DNA and RNA and molecules and physiology and environment are in a constant dance, then we do not assume stable mechanisms. In this
setting we can conceive of environmental perturbation of molecules and pathophysiology, and we can begin to imagine that some perturbations could be dangerous.

Within the genetic narrative, autism is what it is (and has always been), and it will take science to significantly improve the quality of life of affected individuals. Therefore, our agenda should be to provide evidence-based therapies and proceed painstakingly over time to improve what is available through targeted scientific research.

Within the environment narrative, genetics may contribute risk, but the systems output we label “autism” plausibly is occurring more frequently on account of a growing number of environmental exposures, a compromised food supply that is depleting nutrients necessary for physiological resilience and contains additives that when processed by the body may drain its reserves or cause direct harm, major and even radical alterations in activities during infancy and childhood, and probably even epigenetic effects passed on to children from noxious exposures experienced by parents or grandparents. Within this explanatory framework it is to be expected that the increases are being driven by an epidemic of active pathophysiology that in infants and toddlers can lead to autism. This narrative yields an action plan to implement while we wait for targeted science because the processes it describes are amenable to modulation and reduction through measures such as eating a high-nutrient-density, high-antioxidant, and anti-inflammatory diet, encouraging more full-bodied motor activities during early development, and reducing exposures to toxins and infectious agents.

Within the genetic narrative, there is no plausibility either to the claim that autism numbers are rising or the claim that people with autism can lose their diagnoses. Any increase in numbers is dismissed as an artifact, and any child who loses the autism diagnosis is presumed not to have been truly autistic in the first place. When large studies do not yield decisive genetic information, the proposed solution is to increase statistical power by organizing even larger studies. As one of my geneticist friends said to me, “You environmental researchers should just wait for a few years. By then we’ll have worked out what the key genetic features are of autism and then you will have a basis for pursuing environmental research to explain the few residual features not explained by genetics.”

Within the environmental narrative, the increasing reports of reversals of diagnosis (including those in children with rigorous, high-quality clinical evidence of an initial autism diagnosis) are cause for examination of core assumptions and for reshaping research and clinical agendas. These
Addressing an Apparent Epidemic through a Praxis of Environmental Pathophysiology

With autism rates of about 1 in 88 in children and 1 in 54 boys—and probably rising—anything we can do sooner rather than later to stem the tide ought to make eminent public health sense. Given that simple measures like diet, nutrition, avoiding toxins, and rethinking education and pedagogy may help reduce the active pathophysiology that may be aggravating if not causing autism, a strong argument can be made that implementing these measures ought to be primary in a public health approach to autism. Yet this approach is marginalized to a significant degree because it is implausible in a simple gene-brain-behavior narrative.

Many parents of children with autism have implemented these measures on their own and have organized widely to train other parents. They have grown frustrated with the professional care emanating from the genetic narrative’s static encephalopathy-based model of autism. Many perceive that their child is “in there” and feel that physicians and other clinicians are not doing everything they can to rescue their child from what is trapping them in brain and often also body constrictions. Standard medical and behavioral care does not help them with the daily, often excruciating difficulties with sleep, low threshold for intolerance of sensory stimulation, food refusal, and seizures. It offers behavioral therapies that sometimes help a good deal and too often only a little, and it offers pharmaceuticals that also help only sometimes and often lead to nasty side effects, like obesity and hormonal dysregulation.

Countless parents have been denied medical workups for conditions like constipation or esophagitis because “it’s just part of the autism,” with the implicit or explicit inference that since autism is, in the minds of the clinicians, untreatable, anything associated with it is untreatable as well. It should be noted that although doctors who make this claim are generally strong advocates for “evidence-based medicine,” there is no evidence for the claims they are making, and parents often feel that they are actually saying these things to avoid dealing with difficult, unruly, time-consuming, and even perhaps viscerally disturbing patients.

Another issue is that even when professionals take on these complex patients, their treatment armamentarium does not usually include such measures as supporting challenged metabolic pathways except in certain cases (e.g., the use by some but not all specialists of a “mitochondrial
cocktail” of high-dose vitamins and other cofactors in mitochondrial metabolism). The taboos around some of the alternative treatments used by parents have stopped many professionals cold from even familiarizing themselves with the methods and rationales of these approaches. Over time, as success stories have accumulated of children (and even some adults) greatly reducing the severity of their problems and sometimes even losing their diagnoses, some serious scientific attention has begun to be paid to these phenomena. As mentioned earlier, the basic principles of these therapies include tackling subcomponents of “the autism” as problems that can be solved and thereby reducing the stress on the whole system so that it has more of a chance to recalibrate.\textsuperscript{76}

But even if medical professionals were to expand their repertoire and their ability to deal with these challenging patients, I think that the magnitude of the problem exemplified by autism is much bigger than what medical professionals can solve on their own. Today’s typical modern diet and lifestyle are corrupted by poor food, lack of exercise, and chemical exposures through cosmetics, home-care products, household construction materials, and pesticides in the home, school, and workplace. All these and more may well be implicated in running down the body’s systems and creating inflammation, oxidative stress, and mitochondrial strain and dysfunction until all of this finally affects the brain. Given this deeply unfortunate global state of affairs, once we take seriously the role of the environment, we need to come to grips with the magnitude of what we face. A much bigger response is needed than carefully targeted and specific treatments. Doctors do not have time to give transformative teaching on lifestyle changes or address public policy. This will need to involve not just highly trained professionals but also paraprofessionals as well as laypeople—even a social movement to transform unhealthy lifestyles into health-promoting (and sustainable) living habits. Such a broad-based transformational program will work best if we ever can move toward a reasoned dialogue about the predicament we are in.

Once we understand that autism is not genetically inevitable—that it is not a genetic tragedy but an environmental and physiological catastrophe—the point becomes not just to understand autism, but to change how we conduct our lives so that we support health rather than harm.

Beyond Autism

Clearly, gene myths are a problem in autism and are among the forces putting obstacles in the way of implementing a full-force public health
campaign to reduce environmental risks. Clearly also, gene myths are not restricted to autism, although autism is an interesting case study. It is becoming painfully obvious that environmental risks are key players in epidemics of chronic illnesses from cancer and heart disease to diabetes and obesity, and that the active pathophysiological processes involved in autism also are present in these other conditions. The public health measures I am proposing to help reduce autism risk would also reduce risk for many other conditions. Since so many environmentally modulated illnesses are still often considered genetic in origin, people suffering with these problems remain confused and often do not become aware of the self-care measures that could potentially help them greatly.

Shifting from a static genetic model of autism as a lifelong brain defect to a dynamic model of active systems pathophysiology creates a platform for incorporating the contribution of genes into a broader, more inclusive, and more empowering framework. Successes in this shift will have much broader applications beyond autism.

I am grateful to John Elder for his assistance in framing and preparing this chapter.

10. Autism


62. Ibid.
64. Aneja and Tierney, “Autism.”
69. B. N. Ames, I. Elson-Schwab, and E. A. Silver, “High-Dose Vitamin Therapy Stimulates Variant Enzymes with Decreased Coenzyme Binding Affinity


11. The Prospects of Personalized Medicine


2. When the field emerged in the 1950s, researchers initially used the term “pharmacogenetics.” In the 1990s a convergence of interests rebranded the field as “pharmacogenomics.” See Adam M. Hedgecoe, “Terminology and the Construction of Scientific Disciplines: The Case of Pharmacogenomics,” *Science, Technology and Human Values* 28 (2003): 513–537. Although some authors try to distinguish the two terms, they are essentially interchangeable now. Since “pharmacogenomics” is now in wider use, I use that term throughout.


