REVIEW

Learning About Autism

认识自闭症

Aprender sobre el autismo

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ABSTRACT

A medical essay written in 1923 pointed out the fallacy of blaming a chronic illness on the name of a disease. The focus of treatment should be the individual, not the disease. With a focus on options based on the individuality of each patient, I ask a simple two-part question: Does my patient need to avoid or be rid of substances and/or to be provided with substances that would favor nature's impulse toward healing?

In my academic training as a physician, I learned that a clinically effective stance favored an optimistic intent combined with the objective application of my skills—refined though the practice of listening, prescribing, and observing outcome. My understanding of autism has rested on a foundation of the individuality of every living thing, the rhythmicity of life, and the balance that characterizes healthy systems. The first autistic child I examined struck me with a nonverbal message: "I am in here; see me."

The recognition of the role of bacterial toxins amplified my notion that a general disorder of the microbiome underlies the loss of immune tolerance that accompanies the global state of sensitivity found in individuals in the autism spectrum. Depletion of organisms that have populated the human gut since before the dawn of our species arises as the most recent elevation of my learning curve.

摘要

有一篇发表于1923 年的医学论文指出，将慢性病归类为疾病是一种错误的做法。因其治疗的重点应该是个体，而非疾病本身。基于每一位患者个性特征为着眼点的选择，我提出了一个简单的包含两部分的问题：我的病人在避开或摆脱某些物质以及/或获得某些可以使他们产生康复的自然冲动的物质方面是否存在着未被满足的需求？

在我接受一名医师的学术训练期间，我认识到，临床上有效的立场与个人技术的客观应用——对听诊、开处方和观察结果加以有效结合，对实现乐观的目标非常有利。我对自闭症的理解是建立在一切生物体的个性特征、生命的周期以及显示健康系统的平衡的基础之上的。10 我检查的第一个自闭患儿给我留下了深刻的印象，这源于他传递给我的一条非口头信息："我在这里；来看我。"

对细菌毒素作用的认识强化了我的见解，微生物组的广泛失调导致免疫耐受性降低，且伴随着自闭症谱系个体身上发现的整体的敏感状态。因为我们的物种出现在黎明之前我学习作为最新的海拔已填充的生物体，人体肠道的枯竭。

SINOPSIS

Un ensayo médico escrito en 1923 señalaba la falacia que suponía culpar al nombre de una enfermedad de la patología crónica que sufría el enfermo. El objetivo principal del tratamiento debe ser el individuo, no la enfermedad. Manteniendo el centro de atención en las opciones basadas en la individualidad de cada paciente, planteo una sencilla pregunta que consta de dos partes: ¿Tiene mi paciente necesidades no satisfechas que impliquen evitar o dejar de consumir sustancias y/o que se le faciliten sustancias que favorezcan el impulso natural hacia la curación?

En mi formación académica como médico, he aprendido que una estrategia clínicamente eficaz apoyaba un propósito optimista combinado con la aplicación objetiva de mis destrezas, refinadas a través de la práctica de escuchar, recetar y observar los resultados. Mi comprensión del autismo se ha basado en la individualidad de cada ser vivo, la ritmicidad de la vida y el equilibrio que caracteriza a los sistemas sanos.10 El primer niño autista que examiné me impresionó con un mensaje no verbal: "Estoy aquí; entiéndeme".

El reconocimiento del papel de las toxinas bacterianas reforzó la idea que tenía de que un trastorno general del microbioma subyace a la pérdida de la inmunotolerancia que acompaña al estado global de hipersensibilidad que se encuentra en los individuos del espectro autista. El agotamiento de los organismos que han poblado el intestino humano desde antes de los albores de nuestra especie se presenta como el más reciente elevación de mi aprendizaje.

THE PATIENT AS AN INDIVIDUAL

Learning about autism required developing a map of health and illness and navigating patients away from illness and toward health. My map began to take shape in the spring of 1959 in makeshift clinics in the valley of Katmandu, Nepal. My mentor, Edgar Miller, MD, a retired cardiologist from Wilmington, Delaware, had joined the fledgling staff of Shanta Bhavan United Mission Hospital. After each patient visit he posed a question: "Sidney, have we done everything we can for this patient?" His focus on *this patient* centered my map of medicine on the individual patient, where it remains today.

In medical school, I learned another map—arranging illnesses in branches of a taxonomic tree, with disease entities as its terminal twigs. In that paradigm, navigating was linear—grasping the name of my patient's condition, which became the target of treatment. Within that paradigm, the notion that the same treatment might suit different diseases was heresy. At bedside during grand rounds and at clinical pathological conferences, the prize went to the one who best specified the disease. The classification of the patient produces a basis for prognosis based on the expected outcome for members of the patient's group. In the realm of chronic illness, the patient's identity becomes attached to the name of his or her condition. The elements of the patient's story and condition that describe him or her as a unique person ("this patient") become irrelevant and obscured by features that belong to the "disease group" and becomes the basis for giving him or her the group treatment for that disease.

Three years after my work with Dr Miller, my second-year medical classmates and I watched a short film during our psychiatry course at the Yale School of Medicine Child Study Center. The film featured a dignified physician saying to the parents of a developmentally disabled child, "Don't look for answers." After all the dissections, deaths, births, and dramas of medical school, my keenest memory was that to be a good doctor I should learn to say "Don't look for answers," but Dr Miller had gotten to me first. The echo of that film struck me in 1973 during a routine annual examination of Mark, a 13 year-old "profoundly retarded" autistic boy at the residential treatment center where I was a newly minted attending physician. As I approached his right eye with my ophthalmoscope, his lightning-fast fist shattered the bridge of my glasses. It was my first contact with autism, and it kindled my enduring interest. Not during my nosebleed, but in retrospect, I realized that without words Mark had posed a question: "Are you looking into but not seeing me?" Inarticulate, nonverbal Mark had allowed me to hear the "voice" of every nonverbal autistic person I have known since then: "See me; I am in here."

Speaking to autistic children and assuming they understand words, tone, and intention is always a winning proposition, even when they don't appear to be paying attention. If we speak in their presence assuming they understand every word, no words will be wasted. Doing so has never failed, and often succeeded, in helping parents realize a potential in their child that even they had been unaware of. The same rule applies to newborns and the comatose. Physicians from various specialties often are drawn to biochemical, immunological, and toxicological problems of autistic children. They will be rewarded by beginning with three questions: "Am I really seeing him or her?" "What is the best first step for this individual?" and "Have I done everything I can for this patient?"

Parents frequently tell me that their kindly pediatrician has responded to their plea for direction with the question, "So you think you can find a cure for autism?" "No," they say through angry tears, "we just want to help our child." They cannot understand the doctor's inability to see past the child's label and look for causes. Contemporary medicine's map of its universe of diseases is misleading and has allowed him to believe that *the symptoms are the result of the autism.* It is easier to acquire new skills or knowledge in a new field than to replace old knowledge with new ways of thinking.

The Fallacy of Mistaking Names, Ideas, and Things

It fell to me as chief resident in the 1960s to convert the pediatric service to the Weed System of Problem-oriented Medical Records. The students and interns climbed right onboard; the residents and fellows were a bit more challenging. The faculty were resistant to converting the language of medicine to focus on the individual as opposed to the disease. The consequences of that resistance are many, including the notion that because there is no known treatment for autism, parents should not look for answers.

The contemporary medical way of thinking about illness is the greatest obstacle to our understanding of autism. Imagine what would happen if engineers explained the collapse of a bridge was the result of "bridge disease" or a case of "*collapsus pontis*." Do we believe that disease entities exist in nature and leap from their taxonomic trees and attack us? I do believe that language guides thought, and we continue to hear that autism causes the difficulties these children have with speaking, behaving, and interacting. Patients are also asked to believe their depression causes sadness, their arthritis causes joint pain, and asthma causes their wheezing.

DIMENSIONAL THINKING

In 1969, Shannon Brunjes and I were charged by "Fritz" Redlich, MD, the medical dean at Yale University, to use computers to improve patient care— and not just to crunch numbers. Shannon was the computer person, and I the patient care person. Shannon said to me in the first days of my initiation that if medical information were to be "computerized," it should be shaped into rows and columns—starting with two dimensions—like a spreadsheet. The position of each cell would carry the meaning of the word encoded at the intersection of

its defining row and column. Rows would designate locations like *hand*; columns would designate functions like *pain*. A third dimension would name the system, eg, skin or musculoskeletal. A fourth dimension would designate severity and so on. We invited representatives of the medical school's clinical departments to join us in building a lexicon of each specialty's language so that we could encode its words into the multidimensional system. The project ended like the tower of Babel. The foundation of the tower remained, however, in the understanding that the task was to give medical descriptors a novel dimensional system to encode their meaning. The tower failed by having a committee as its architect, and building materials (words) scavenged from outdated systems of classification.

Shannon directed me to an appendix in the linguistics classic *The Meaning of Meaning* by Ogden and Richards (1923). An essay by Francis Crookshank, MD (1873-1933), the controversial British epidemiologist and medical and psychological writer, created for me a moment after which nothing would ever be the same. After reading that "Medical students fondly believe that diseases were discovered by their professors as was America by Columbus," I grasped the distinction made between names, notions, and *t*hings, and the fallacy of confusing name with cause. The diagnostic salad of disease entity, comorbidity, and autism is the product of faulty logic.

In the 1970s while I was an attending physician in the Pediatric Neurology Clinic at Yale treating children with seizures and allergies, there were more than 100 cases of food allergy–induced seizures reported in the neurology literature. I was in need of a new approach. The orthomolecular psychiatry movement, the American Academy of Environmental Medicine, and the Autism Research Institute (ARI) helped develop practical approaches to the immunology, biochemistry, and toxicology of neurological disorders and support research (Figure 1).

From the research community with sponsorship from ARI for 15 years, pioneers came who assembled and provided biochemical details—Jon Pangborn, PhD, Richard Deth, PhD; S. Jill James, PhD; and others helped us make sense of the biochemical core of autism's pathology. Dr Pangborn advanced our understanding of the physiological biochemistry of amino acids, neurotransmitters, sulfation, and methylation chemistry. Dr Deth documented the ways that environmental toxins, especially lead and mercury, impair remethylation of homocysteine. They do this by oxidative damage to methyl cobalmin and the consequent harm to dopamine D-4 receptor site. This has implication for attention. Dr James and her team documented the ways in which the decreased levels of reduced glutathione (GSH) lead to failed resuscitation of methyl cobalamin in autistic children. A repertoire of interventions grew from the collective clinical experience on the part of practitioners who used the "Defeat Autism Now! (DAN!) Protocol."

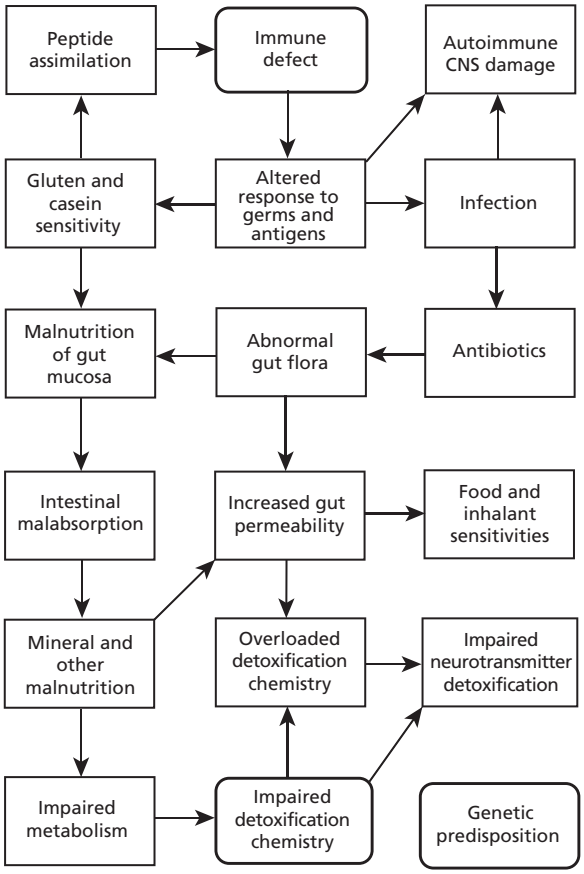

Figure 1 Taken from the Consensus report,[1] this diagram reflects interactions among etiologic factors identified by parents, practitioners, and researches who gathered in 1995 for consideration in both clinical and research settings.

Abbreviation: CNS, central nervous system.

METHYLATION AND SULFATION

The interplay of empirical observation and hard science demonstrated the role of folic acid in the prevention of midline birth defects. Alerted by the early observations of Smithells,[1] I learned of Butterworth's early report[2] of reversal of cervical metaplasia using high-dose folate. I found that 20-mg daily supplements never failed to reverse persistent cervical metaplasia. I learned enough about folic acid to advise Rimland, MD, that it might help treat the hyperactivity reported by parents who had found di-methylglycine helpful in improving speech and behavior in their autistic children. Subsequently, a visit from Paul Cheney, MD, PhD, clinical research pioneer in chronic fatigue syndrome (CFS), compared his observations on the biochemistry of patients with CFS with what I had observed in autistic children. We agreed that the biochemistry and immunology of autism and CFS were hauntingly similar.

Vitamin B_6, the cofactor for cystathionine beta synthase (CBS), is part of the methylation-sulfation chemistry that Dr James elaborated on that began with parental reports of vitamin B_6 supplementation in Dr Rimland's parent surveys. Hyperactivity was a vexing companion to the benefits noted by parents. Adelle Davis, the pio-

neer who popularized nutritional approaches to chronic illness remarked in a conversation with Dr Rimland that the B_6-related hyperactivity would respond to magnesium. This became part of the early pair—B_6 and dimethylglycine (DMG)—of remedies that was first validated in the experience of parents gathered and given weight by Dr Rimland's review of the supporting literature.

AUTISM 360

In 1978, I restarted a previous effort to create a database of information about autism from scratch using the words not of professors but of patients. I built a lexicon from every word of every patient who consulted me over nearly 2 decades in a general practice that focused on complex chronic illnesses. I encoded the meaning of every word of my patient's narrative as an intersection in multidimensional space and designed a computer application that let physicians and their staff members capture the entire narrative of their patients. A report was created that allowed the patient to see himself (and be seen) in all its defining detail. Medigenesis, a generalized medical Internet-based system was used to create a specialized application, Autism360.org, to serve the needs of the global autism community.

When "spectrum" entered common parlance to refer to varying degrees of severity of autism, Medigenesis already had a place for every nuance of medical description patients might use to express their individuality.[3] Autism360 created a highly structured database of all the words thousands of parents used to describe the strengths and symptoms of their autistic children within the conceptual space of "spectrum." Parents and practitioners now have a full portrait of the details that describe a child as an individual and provides precision for describing both individual and collective patterns clinical history, finding, and laboratory tests.

NEW PARADIGM

Science deals with entities, facts, substances, forces, and the words and numbers that capture their granularity. When we listen to patients, their narrative and laboratory data constitute the granular data upon which decisions will be based. The mistake of explaining problems of speech, behavior, interaction with others, and sensitivities in chronic illness as being caused by autism is nearly universal in both lay and professional speech. The details of the narratives and lab data of our patients produced questions that began with "could." Two simple questions, learned from the stories of patients, gave me a new paradigm. In that paradigm, autism was not a specific, rare, lifelong, incurable disease of early childhood caused by cold mothers (and later by genetics) that occupied the tip of a branch of the classification of childhood diseases.

During a routine history from the father of a family joining my family practice in a new pre-paid health plan in New Haven in 1971, I asked the question "Any allergies?" "Egg" was his reply. Noting it in his record, I asked, "What happens if you eat eggs?" The story he told with precision was one of sudden pain, prostration, and digestive distress. Tasting a dish inadvertently stirred with a fork bearing traces of egg might put him on a dining room floor. If he could have such violent symptoms from ingesting a tiny taste of egg, there might be other patients, perhaps ones with chronic illnesses, who suffered from all manner of symptoms without suspecting the symptoms might be prevented or ameliorated by avoiding or eliminating certain substances. The answer to a question that begins with "could" is "yes." The probability of a connection between a symptom and a specific exposure may be tiny. It takes only seconds to comment on the possibility in the course of a medical conversation.

For example, a patient's problem with a chronic symptom might come as a response to something in the patient's diet. Even if the odds are long, the patient is curious to know how we would discover such a proposition. The value of this proposition is increased by the context of a child who is sensitive to many stimuli. How can we test for such a connection? After decades of practice and research in the art and science of sensitivities and an affiliation with the American Academy of Environmental Medicine, I believe the usual simple answer is 5 days of avoiding the suspect factor, then a challenging exposure, then the patient gives a "thumbs up" or "thumbs down."

The complexities of identifying substances to which a patient is sensitive are irrelevant to the question: "Could this person have an unmet need to avoid or be rid of something to favor nature's impulse toward healing?" The value of the question is independent of the fact that the answer is always *yes* and may lead to cures more often than suspected. There are patient with chronic illnesses that can be cured by discovering and addressing a hidden intolerance.

An even higher value, however, comes when the focus of the conversation switches away from a focus on the diagnosis to the individual, creating a conceptual space where parents, patients, and I could collaborate to look for answers. In the clinical domain of autism where sensitivity is a prominent theme that embraces many symptoms, the answers and the results of interventions are most productive. When someone is notoriously sensitive, it is sensible to avoid stimuli that provoke negative reactions. Another value of considering sensitivities in an autistic child with many overt sensitivities is to shift the question from "what?" to "why?" Before describing how the "why" question entered my learning process, let me introduce the converse of the "could . . . avoid" question: "Could this patient have an unmet special need to get something which if supplied might hasten nature's strong forces toward healing?"

CASE REPORT

Antoinette was a single working mother of two children. I was pleased in the early months of my family practice to offer her reassurance that her headaches had a name—migraine—and that the neurolo-

gist I referred her to would find the right treatment. Each medication disagreed with her more than the previous, and none removed the menace of periodic and premenstrual migraine so disabling that it threatened her livelihood. After some months she let me know, apologetically, that she had sought the advice of a chiropractor outside the coverage of our plan. He had tested her by means I assumed to be sheer quackery, then prescribed a supplement of vitamin B_6 and magnesium that completely solved her problem. Thus began my quest to learn things about nutritional biochemistry I had missed at Yale.

When I described to my colleagues what I had learned from my patient with egg sensitivity or from Antoinette, I discovered an abyss. "Are you claiming that colitis is caused by food allergy? Do you mean to say that vitamin B_6 and magnesium are the cure for migraine?" The gap between "name-it, blame-it" disease-based medical thinking and lessons learned from my anecdotes could not be closed by my insistence that I was talking about a treatment for one person, not claiming to generalize it to his or her disorder.

I took the directorship of the Gesell Institute of Child Development in New Haven in 1978. Arnold Gesell, MD, had been a major voice in the documentation of individual rhythms of child development. The behavioral assessments he charted were designed to provide physicians, teachers, and others with measures to offer a biological perspective on a child's individual path. Not long before my move to the Gesell Institute, I attended a meeting at the Yale Child Study Center with Dr Rimland. His scholarly book *Infantile Autism* had convinced a growing majority of experts that autism's causes were biological, not psychological. Dr Rimland presented his rationale and the results of parent surveys of treatments that worked, had no effect, or had negative effect in their autistic children. He revisited evidence that released autism from the grip of those who had named "refrigerator mothers" as a key etiologic force. He presented data supporting biologically based interventions such as avoidance of foods and toxins and addition of supplements. The conference took on an uneasy feeling, and Dr Rimland received an unwelcomed academic reception as he carried his listeners to conclusions regarding the biology of autism. Dr Rimland and I were thereafter friends, sharing the belief that the voice of parents should be heard and that the data of that collective voice should talk.

One day in 1994, Dr Rimland stopped by my office and listened to my report of the striking responses to the prescription of antifungal medications over the previous 15 years. It began with a little girl whose autism was cured when I prescribed oral nystatin powder aimed at an intestinal yeast problem that frequently underlies childhood eczema and other allergies. (Her eczema and autistic symptoms had appeared following courses of antibiotics for recurring ear infections.) I remembered that Dr Rimland's surveys reported that thousands of parents had consistently placed the antifungal medication nystatin at the top of the list of pharmaceuticals ranked by their ratio of positive to negative effects. These findings raised questions regarding the immunological, biochemical, and toxicological aspects of autism.

In 1995, Dr Rimland and I organized the first of many meetings on autism with the support of Candace, the mother of an autistic boy. Thirty practitioners, scientists, and parents from around the world gathered to find common ground. The ethos of that original meeting and all subsequent annual and then twice-yearly conferences under the aegis of ARI established the value of an exchange among parents, practitioners, and researchers representing diverse interests and specialties.[4-6] In the subsequent decade, leading scientists, innovative practitioners, and brilliant parents joined our meetings. Three words crept into the conversation: *epidemic*, *biomedical*, and *spectrum*. "Epidemic" burst through a barrier of denial that still exists. "Biomedical" appeared to occupy a body of practice outside genetics, pharmacology and psychology. "Spectrum," on the other hand, slid easily into the vocabulary of parents, practitioners, and scientists interested in autism. Suddenly the collective struggle to understand autism had been given a transformative word. First published by Gillberg,[7] whose gift of this word had lain unused for a more than a decade, "spectrum" will naturally spread to other diseases as it did with autism. As the word spreads, so will a shift toward dimensional thinking about all illness. The word *spectrum* provides an apt metaphor for the variety of individuals who carry the gist that acquires the label. For parents, however, the use of the word *spectrum* rather than a specific *entity* deprived them of the relief that comes with the pronouncement that "we know exactly what is wrong." It propelled them deeper into relief's constant partner, grief: the child was not found but lost with no clear exit.

THE IMPORTANCE OF DETAILS

Having these descriptions in words and graphics with the ability to track treatment responses over time clarifies what can otherwise be a confusing temporal landscape. Accessibility of descriptive details also helps focus on the individual's concrete symptoms as opposed to the abstraction of a diagnostic label. Moreover, the details form patterns that reveal both clinical options for intervention and indicators of progress detected in changes in hair, skin, bowels, sleep, or odors beyond the focus on the defining symptoms of autism. Such details are also very relevant to the biochemistry, immunology, and toxicology of autism. They may represent features of neuromuscular irritability, loss of immune tolerance, or mechanisms of inflammation or intoxication that are upstaged by global problems in cognition, expression, or behavior. Itching, sneezing, congestion, rashes, and redness are messages from the body signifying loss of immune tolerance. Constipation, cold hands and feet, twitching, anxiety, and sleep problems are indications of neuromuscular irritability that may

reflect unmet needs for magnesium. Dry, cracking skin; lackluster hair; dandruff; and patchy dullness are signs of unmet needs for omega-3 fatty acids.

Attending to these signals is not a treatment for autism. It is a response to the question of whether we are doing everything we can for this patient. Letting the data talk is a phrase that—at the level of the individual—says that information technology can present crisp, detailed, well-organized data so that the patient is seen as an individual with all the particulars, including strengths and skills while not being blinded by a diagnostic label. This is very different from focusing on the problems that give a group of people a diagnostic label and helps to keep the focus on treating the patient as opposed to the disease. "Autism Spectrum Disorder" can help us recognize each individual by the system, function, location, severity, onset, frequency, duration, and aggravating and alleviating factors that characterize him or her.

Letting the data talk is also relevant at the level where we can detect patterns formed in the conceptual space where individual and collective data interact. The interaction is the formation of clusters based on proximity (similarity) or distance (difference) in the individual data. In Autism360, proximity analysis offers each user the opportunity to learn from very similar individuals about treatment options that worked or failed.

The new metaphor of "spectrum" and the information system for representing actual experience of patients replace the old metaphor of disease entities and classifications based on abstractions. This helps us listen to patients in ways that allow us to hear what they want to say as opposed to hearing only answers to questions we want to ask.

MAGNESIUM

There are an infinite variety of people but relatively few things that can go wrong with them to produce chronic illness in a given environment. Leo Galland, MD, now an author and integrative medicine practitioner in Manhattan, joined the medical staff of the Gesell Institute in New Haven in 1979. In 1981, Dr Galland noted that magnesium was one of the core therapeutic options for patients with a very wide assortment of diseases from tooth grinding to mitral valve prolapse or from loud noise sensitivity to constipation. In 1991, I reported the study of symptom patterns in my patients with differing results in their magnesium loading tests to show the value of my system for coding symptoms to reveal patterns that could not be discovered by other means.[3] A subgroup of individuals with paradoxical magnesium wasting had low instead of high blood pressure and a distinctive pattern of emotional symptoms (anxiety and depression) compared with patients with the typical feature of retention of an intramuscular load of magnesium. The discomfort of a magnesium injection is a barrier to finding such a subgroup among autistic children. The theme of neuromuscular irritability that runs through the symptom profiles of autistic individuals and the calming effect of magnesium supplementation up to doses that approach bowel tolerance (just short of provoking bowel movements that are too loose or frequent) are hidden from those who have not learned that an empirical trial—a "thumbs up or down" test—may be the best measure of need.

FATTY ACIDS

Before electricity, light was produced by oils—a source of calories when burned in the body's metabolic fire. Only recently have we begun to understand their roles as the substance of the membranes that enclose every cell and their importance to cellular function and prostaglandin hormone synthesis. The pathology of unmet needs for omega 3 fatty acids was a feature of our regional quarterly seminar with Drs Leo Galland, David Horrobin, and Donald Rudin. Dr Rudin's team was the first to synthesize the double-layered lipid cell membrane, and he was an advocate for the role of omega 3 fatty acids[8] along with the studies[9] of Andrew Stoll, MD, showing benefits of high-dose omega 3 oils to patients with bipolar disease. I reported a case involving a boy from Indiana with intractable headaches. An anomalous metabolism of omega 3 fatty acids documented in Dr Horrobin's laboratory gave the answer to his problem.[10] The patient's mother, Laura Stevens, went on to earn a doctorate in biochemistry and published the first report[11] of the use of omega 3 oils in attention deficit disorders that provided a reasonable basis for understanding the importance of fish oils in children with autism.

AN UMBRELLA AND A BENCH FOR COMMON GROUND

The opening words of the autoimmunity conference in 2007 were spoken by Yehuda Shoenfeld, MD, incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Sackler Faculty of Medicine, Tel-Aviv University, from his book *Infection and Autoimmunity*.

> *While some would say that everything is autoimmune until proven otherwise, reading the chapters in this book written by world leaders in autoimmunity brings one to the conclusion that everything after all is infectious until proven otherwise (including autoimmune diseases).*[12]

If all chronic illnesses are autoimmune and autism is now well established as a chronic illness, then autism must have sufficient features of autoimmunity to justify measures aimed at the restoration of immune tolerance. Chronic illnesses share the same features of inflammation, oxidative stress, and problems with detoxification, all conditions involving impairment of GSH synthesis. The work of Drs James and Deth—outlined in this issue—become a framework for evaluating autism (Figure 2).

This established the equivalent of a fundamental principle providing firmer support for a patient-centered decision than clinical trial data for which we

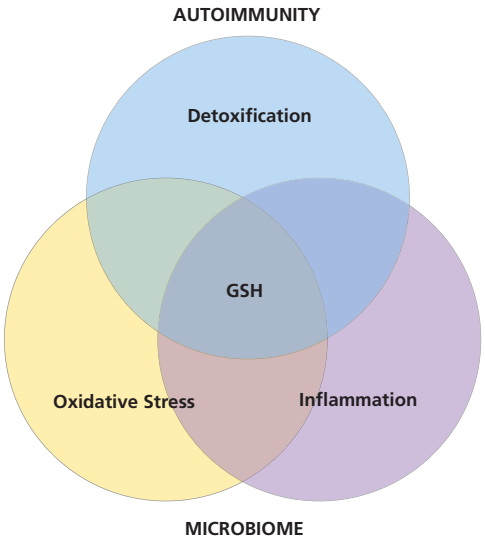

Figure 2 The Venn diagram indicates the central role of mechanisms related to glutathione in chronic illness. Autoimmunity and the microbiome illustrate the calls for clinical attention to the restoration of immune tolerance in part through the restoration of the gastrointestinal microbiome.

Abbreviation: GSH, glutathione.

might have to wait for years. A parallel line of validation applies to the microbiome underlying the Venn diagram outlined above. Within the past 5 years, Derrick MacFabe's demonstration of the mechanisms of propionic acid from an altered microbiome that can damage membrane structures and related carnitine function has become relevant beyond the field of autism to various aspects of health and human development. His research[13] teaches us that some combination of l-carnitine and acetly-l-carnitine supplementation is likely to be beneficial to some autistic children. There is a relationship between toxins produced by the gut, their relative impact on carnitine metabolism, and the issue of broad-based sensitivity that characterize the reactions of autistic patients to the environment.

SENSITIVITY

Sensitivity is evident whenever it is recognized by patients and is familiar to any clinician who asks about patients' intolerances. A heavy exposure, particularly during stress, is a common factor but the etiology of the phenomenon remains obscure. Shoenfeld's thesis, as detailed in *Infection and Autoimmunity*, is that sensitivity as manifested in autoimmunity is engendered by instances of mistaken identity originating with antigenic similarities among germs, tissues, foods and other environmental factors that should be benign. The clinician stands between a patient's sensitivity and the complexity of putative toxins/antigens and is unlikely to find therapeutic choices in laboratory measurements. Standing in the midst of this lack of clarity, clinicians can only depend on simple, short, relatively safe interventions. A 20-day trial of an antifungal, antibacterial, probiotic, or other measure to influence the microbiome with the patient as the best laboratory is the alternative to inaction given the lack of evidence-based options. Dramatic results tend to come from the far ends of the normal distribution curve where dramatic results in dire situations and document possibilities that may not be able to be duplicated.

CASE REPORT

"Jack" was a 20-month-old boy who had not gained any weight for 6 months when he came for a consultation. He was moaning—in constant gastrointestinal pain, and he needed to be propped up in the arms of his mom or dad to deal with reflux. He was intolerant to all but three foods. He had been unresponsive to trials of anti-inflammatory drugs, H2 blockers, and cromoglycate. He had more than enough symptoms even at his young age to place him in the autism spectrum. He had a history of antibiotics preceding the onset of his problems. Die-off reactions to *Saccharomyces boulardii* and then to amphotericin B could not be controlled by activated charcoal and could not be endured because of his precarious nutritional status. If, as a matter of principle, his condition had significant autoimmune features, then a trial of *Trichuris suis ova* (TSO) might rescue him. A single fractional dose provoked a wrenching exacerbation of his distress that lasted 4 weeks. His intolerance to just about every food or medication or supplement that he had ever tried was an obstacle to fine-tuning. I had no other good option and prescribed a dose of mebendazole to have on hand if the situation passed some further point of intolerability. A phone call on a Monday night brought us to that point. I asked his parents if they could wait one more day because I did not have a good option and I knew that the reaction was an indication that we had caught his immune system's attention. The next day, he broke through and never looked back. With some fine-tuning, he became asymptomatic over the next few weeks and except for a little reflux, became a healthy, happy, developmentally normal child who climbed right back from 6 months of a flat horizontal growth curve to a prompt reassuring catch-up. Before and after my experience with Jack, I have witnessed the efficacy of helminthic therapy in many patients with diverse problems. In terms of my learning curve in the treatment of children in the autism spectrum, no other form of evidence could replace the lessons learned from Jack.

The decision to give TSO to Jack was driven by desperation, a key lesson learned from taking care of patients far from the middle of a normal distribution curve. My choice of TSO was aimed at a morass of symptoms of immune intolerance. If restoration of immune tolerance could be achieved with TSO, it was worth a try: simple as that.

LEARNING THE HARD WAY

My experience with Jack was hard: on him, on his parents, and on me. I will never forget the anguish of those few weeks with a very sick boy and his parents

on the phone 3000 miles away. There is another hard way of learning. Dr MacFabe does it, and I have been the beneficiary as has been the community of my patients and those of others around the world. Dr MacFabe began with an idea about a molecule with three carbon atoms and followed paths in multiple directions after documenting autistic behaviors in rats, carefully documented: painstaking, systematic, exhaustive, and fruitful. The prize from Dr MacFabe's work is the knowledge clinicians and researchers can share to the benefit of recipients of well-reasoned doses of acetyl l carnitine and carnitine. The article in which Dr MacFabe presented the tracery of his paths at his lecture in Stockholm in May of 2012 is the foundation upon which he has written a more narrative description of his journey in the pages of this issue of *Global Advances in Health and Medicine.*[14]

SUPERPARENTS

Taking care of children in the autism spectrum has brought me close to many extraordinary parents. The moms have been the ones who have generally extended their skills in other fields to biochemistry, immunology, and toxicology. No parent has taught me more than Dr Pangborn with exhaustive support from his wife, Chris, a cofounder of the DAN! movement. His relentless pursuits have yielded a harvest from the published literature and his own consultations with physicians trying to understand the options presented by the laboratories that have joined in the effort to weigh the markers of dysbiosis, heavy metal toxicity, and oxidative stress, not to mention problems with sulfation and methylation, and evidence of poor digestion, assimilation, and metabolism of nutrients and accessory nutritional factors. Susan Owens, a mom without formal training in biochemistry, has brought to the autism community a phenomenon that stands out above the collective success of the collaboration among parents, practitioners, and researchers in the DAN! movement. I have been the recipient to date of 12 129 emails in the exchange she has fostered among parents in the complex subject of the interactions among diet, the microbiome, metabolism, excretion, and impact of oxalates. Of all of the subjects I have tried and failed to master in my efforts to learn about autism, the one Susan Owens took on and continues to explore has been and remains the most vexing. For all the criticism of her project that can be found on the Internet, the sheer volume of opinions voiced on her LISTSERV speaks to us of a need to let data talk about options for parents and practitioners looking for answers.

THE TARGETS OF TOXINS

A vast assortment of environmental toxins, allergens, and microbial products set up an inflammatory response based on toxic or autoimmune mechanism. Signals transmitted via the autonomic nervous system result in distortion of its rhythmic regulator function, give rise to difficulties with articulation and coordination of other movements in the digestive and neuromuscular systems, and explain many of the symptoms found in the autism spectrum.

Therapies aimed at preventing injury to the bowel-blood barrier with avoidance of environmental toxins and removal of resulting toxins such as those derived from gluten and from abnormal gut flora as well as measures aimed at detoxification and repair of damage to energy metabolism and vicious cycles in methylation, sulfation, and GSH production make sense. That sense must be understood within the framework of recognizing that autism—and all chronic illnesses—is a systems problem such as portrayed in the interconnection of Figure 1.

Certain structures in parts of the mid-brain ("reptilian" brain) are functionally outside the blood-brain barrier so that they can "taste" the blood for signals. Dr McGinnis and his coauthors provide a strong argument for the importance of the natural openness to the blood of mid-brain structures that are responsible for autonomic regulatory functions.[15]

When confronted by a systems problem, we are confined to a large extent to a linear process of tailoring therapy to the individual. We can expect, however, that the priorities we choose will benefit from nature's capacity to spread benign influences throughout biological systems just as malign signals can push our virtuous cycles down into vicious ones.

LETTING THE DATA TALK

The parent survey of parents in the 1960s by Dr Rimland are unsurpassed in the realm of letting data talk.[16] Summarized in publications and on the ARI website, they are the richest resource for parents navigating the landscape of a systems problem in which solutions are often restricted to singular, sequential trials to avoid confusion produced by negative effects. The single numeric value incorporating the measure for risk has been and remains one of the most efficient tools any of us has employed for learning about autism. Autism360.org adopted the same device in parental ratings of treatments that have in the 4 years of our operation grown to more than 13 000; a number reflecting the breakdown into seven categories of treatment response. Letting the data talk may never substitute for the power of stories such as Jack's or of carefully designed studies such as those of Dr James. The view provided by Autism360, on the other hand, provides a means for otherwise invisibly large patterns to present answers to questions we could not otherwise ask. These patterns reflect in two directions. First, the users of the website created with funds donated by The Moody's Foundation and a gift of the use of technology from Medigenesis are able to see a clear, orderly presentation of the details they have chosen to represent the individuality of their children or themselves. This presentation along with ratings of treatment options from the cluster of others most closely matching the user's data takes the focus away from treating autism to that of tailoring treatment options to the individual. By simply assembling the description of all of their chil-

dren's strengths, symptoms, exposures, life events, and (with funding soon) laboratory data, users are able to see their children's or their own picture in a new way. The scale of the problem is reduced to granular details that carry the force of decisions aimed at problems of digestion, neuromuscular irritability, and loss of immune and sensory tolerance.

Autism360 reflects images in a second direction—away from the individual toward a collective picture that has previously not been obtainable for a group of individuals who share certain diagnostic features. These cluster-mates also have profiles whose diversity offers ways of learning about what may be called the big picture. Such a big picture may provide, for example, an understanding of gender differences by revealing patterns that could not be seen with the naked eye of practitioners even if their clinical experience covered hundreds of individuals. In 2003, I asked parents if they believed that boys and girls differ in their places within the autism spectrum of symptoms or lab data. There was general agreement with the proposition that boys and girls were very different. The question "In what specific ways?" rendered silence. Recent publication of a "high-altitude" view of those differences[17] and subsequently of a detailed analysis[18] has revealed that boys and girls are not very different and have specified the precise ways in which they are. With the growth of membership in Autism360 from the current level of 5000 to, say, 20000, we will have a richer view of patterns that let the data talk, especially about outliers who are often the source of insight that cannot be found nearer the center of the normal distribution curves.

SUMMARY

Since its first description as a disease entity, autism has been a matter of controversy and shifts in belief with regard to its etiology and treatment. The former has gone from blaming mothers to genetics and now to epigenetic and environmental factors that may account for themes that lie beneath its traditional diagnostic criteria. Autism is unique, so far, among medical conditions in having acquired the attachment of "spectrum" to its nomenclature. The implication of place in spectrum has been confined to a vague sense of high vs low function. The clustering of different individuals reveals patterns based on detailed descriptions of strengths and symptoms rather than diagnostic features. A system that classifies individuals according to diagnostic criteria provides traps of circularity while removing—to be specific—descriptions of gastrointestinal, immune, and other systemic abnormalities of etiologic and therapeutic significance. The clinicians and researchers who have joined in describing the ways we have learned about autism have shared a fruitful process. The search for common ground begun in Dallas in 1995 has rendered a vision of a pattern of interacting factors that none of us brought into the room when we first gathered. Our subsequent development of the diagram in Figure 1 and consensus[1] has provided a leap of learning and understanding that none of us could have achieved alone. You, the reader, may be inspired to such insights or observations by the narratives in the collection of articles found in this issue of *Global Advances in Health and Medicine*. For my own part and from what I assume to be the message conveyed by the coauthors of this collection, I believe that bonds of friendship and participation in a group of diversely skilled parents, patients, practitioners, and researchers is the most efficient path to learning.

Let us, however, heed the prediction of Ray Kurzweil, noted futurist and author, that the merging trends in human and machine intelligence will soon reach a point (singularity) in which the rate of learning will change from linear to exponential.[19] His prediction will come true in fields like autism only if the data on which those intelligences depend are accurate, detailed, structured, and coded from sources (patients, parents, practitioners, laboratories) that have a personal stake and role in their validation and the immediate benefit of being seen not as a diagnosis but as an individual: the target of treatment.

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