THE COSTS AND BENEFITS OF STICKY MOLECULES

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INTRODUCTION

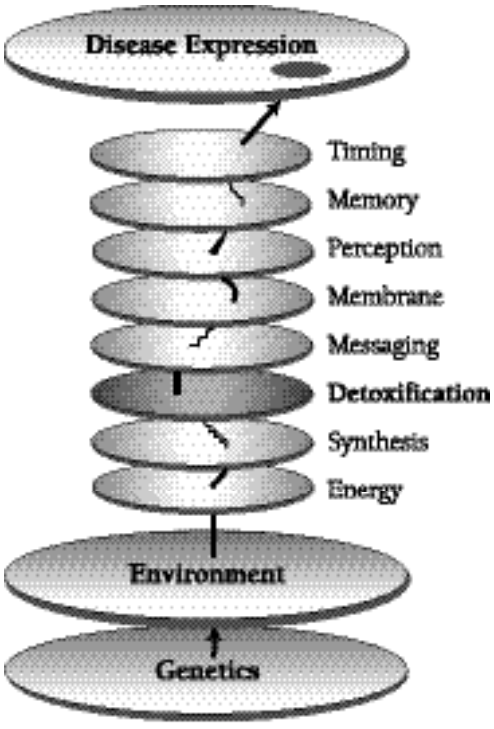
The current epidemic of autism has environmental origins and a biochemical signature. How do these origins and that signature express themselves among individuals who appear to be spared from the epidemic, but who may, in fact, express different variations on the epidemic's theme? In confronting that question in our various patients, we may consider the chemistry of thiols and their role in providing adhesive molecular influence.

FAILURE TO THRIVE

No patient ever came to my office with the chief complaint, "Sid, I am just not anabolizing well." However, many patients complain that they do not have enough energy. Their complaint of fatigue may translate, more or less directly, into an inquiry about the efficiency with which they are recovering the sun's energy from the sugars, starches, and fats in their diet—along the lines of my previous discussion (see IMCJ 3.3) in this series of commentaries regarding the energy "lens." How do we clinicians explore the efficiency and net output of our patients' anabolic efforts to make new molecules?

A sagging growth curve is a defining tip-off of a condition in children that has been dignified with the diagnostic phrase, "failure to thrive." Subtle abnormalities precede the sag, which in any given child may be associated with renal, cardiac or other organ failure, inadequate nutrition, poor nurture, malabsorption, effects of unmet special needs, or exposure to environmental toxins or allergens. In adults, the achievement of full stature leaves the clinician deprived of growth as an indicator, so he must rely on more hidden indicators of metabolic or immune dysfunction.

Normal growth demands the highest "energy tax" in childhood. In adults, the metabolic cost of molecule synthesis of detoxification exceeds that of regeneration and repair. Detoxification requires the synthesis of new molecules, such as urea for the disposal of leftover nitrogen, and the hydrophilic glucuronides, sulfates, methylates, acetates, mercapturates, and glycinates required to detoxify both xenobiotic and discarded endogenous molecules. My next Lenses essay will discuss detoxification as a synthetic process, with its own very large energy budget and its own realm of therapeutics detoxification.



Key Words:

mercaptan (mer·cap·tan), noun, etymology: German, from Danish, from medieval Latin mercurium captans, literally, seizing mercury: any of various compounds that contain a thiol functional group, see THIOL (Merriam Webster-Online).

thiol (thi·ol), noun, etymology: International Scientific Vocabulary thi- + -ol: any of various compounds having the general formula RSH which are analogous to alcohols, but in which sulfur replaces the oxygen of the hydroxyl group and which have disagreeable odors. (Merriam-Webster Online.)

An adult who is not thriving doesn't have growth failure to use as an indicator, but he or she has the advantage of self-expression. A detailed questionnaire augmented by a leisurely intelligent conversation between a symptomatic adult and a physician—plus some laboratory studies—should reveal a pattern of details that permit naming the problem and provide clues about underlying metabolic or immunological problems. Our integrative medical paradigm moves beyond assigning causality to the name of the problem ("your sadness is caused by depression"; "your joint inflammation is caused by arthritis"), and seeks to repair disorder at the deepest stratum of metabolic mischief that is accessible to therapeutic intervention. This level may, at times, be quite simple and superficial (eg, remove gluten from your diet, take a supplement of fish oils, or undertake a short course of antifungals and a yeast/mold-free diet). For delving deeper into complex patient issues, each of us has our own process for peeling away the layers as far as logic, intuition, and the facts will take us, and depending on whether the maps of our clinical landscapes consist of energy fields, meridians, chakras, subluxations, psychodynamics, toxicology, immunology, or biochemistry. The focus of this essay is on the latter three, illuminated by the light of current deepening knowledge of the lower strata underlying the biochemistry of those children caught in the epidemic of autism.

The Metabolic Costs of Stickiness

In deep strata of basic intermediary metabolism, we encounter the sticky and stinky molecules that bear sulfur. The sticky properties of sulfur (familiar to those of us who handle garlic in the kitchen) are related to the odoriferous properties of compounds that contain sulfur. From floral to fecal (but not fishy—those are amines), our olfactory sense is touched by molecules that carry a sulfur atom, whose properties awaken receptors that attract or repel us. The same properties, taken to a less subtle extreme, account for the adhesive properties of sulfhydryl bonds responsible for their role in binding toxins and shaping proteins.

The sulfur system is an orphan. You will find neither a chapter in a biochemical text, nor a scientific journal, nor the concept of an integrated pathology of thiols and sulfates.[1] Such a pathology is emerging from a decade of clinical observation and very recent studies of autistic children, in the context of the current epidemic in which rates of autism have risen more than ten-fold over the past decade or so. Figure 1 shows the center of the core chemistry of the epidemic, in which the genomics and toxicology of sulfur metabolism have combined to sicken many children who have then benefited from nutrients and accessory nutritional factors around this chemistry. These benefits have spurred collaboration among researchers who have documented abnormalities of the substrates and enzymes in autistic children, in and around this chemistry.[2]

The purpose of this essay is not to detail these abnormalities, but to alert clinicians to the notion that whatever is going on in the autism epidemic is likely to be manifesting as other forms in individuals with other expressions of illness. If we look at our patients through the lens of this perception, we will hasten the discovery, in diverse patients, of a pathological thread that is in common with autistic children. These children are the canaries in our coal

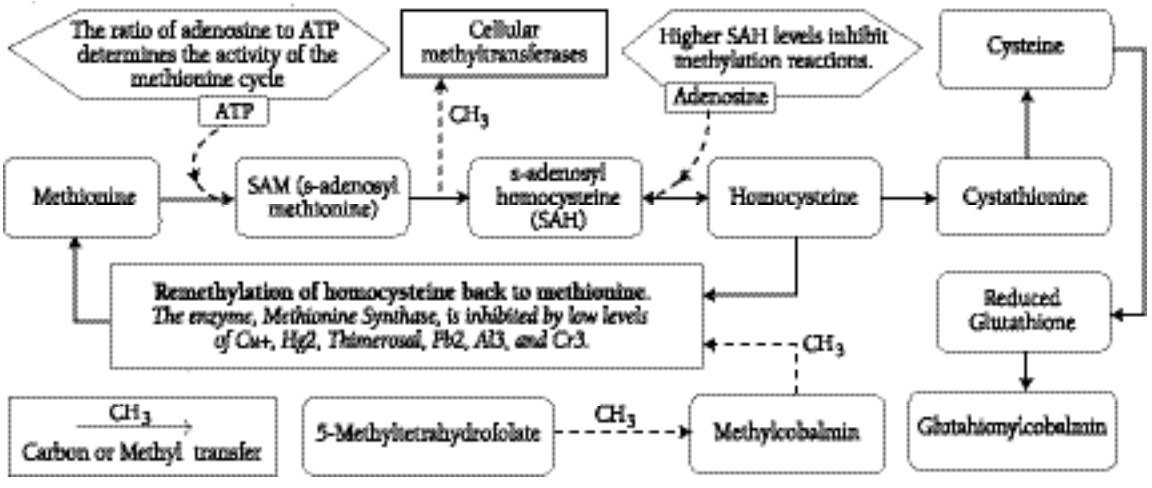


FIGURE 1 The Methionine–Homocysteine Cycle

(Adapted from Baker SM, Pangborn J, Deth R, Owens S, Lonsdale D, Haley B. "The Chemistry of Autism," presented at the Autism Research Institute's Defeat Autism Now! Conference, Philadelphia, PA, May 2003, revised 2004. Diagram and accompanying text by J. Panborn, PhD, available by email from sidneymb@aol.com.)

mine. Our loss will be minimized if we heed the warning of their illness, with specific attention to its toxicology, biochemistry, and remediation. Surely, they are not the only members of our culture to be suffering from the environmental disaster of which they are the chief, but not exclusive, victims.

Here is how my understanding of thiol chemistry entered into my thinking, regarding a patient with autism. Sara is a teenager with a dreamy, distracted affect, repetitive self-talk, and a paucity of spontaneous language. She gets high grades in a classroom of normal children who adore her. Before initiating a "specific carbohydrate diet,"[3] I had obtained a 24-hour urinary amino-acid profile. This test is a good measure of overall catabolic efficiency, analogous to taking inventory of the dumpsters of manufacturing establishments. A couple of years of correlating the profit-and-loss statement of shoe factories, with details of the waste materials of those factories, would yield expertise in using dumpster analysis as an indicator of synthetic effectiveness. Like excess proline in a patient's urine, an excess of soles, heels, or glue could show spillage from an impaired synthetic process of shoemaking. Low levels of cystine and cystathionine (common in autistic children) may show an imbalance in supply and demand.

Sara's studies yielded very elevated proline levels (32.9 mmol/24 hr) (normal <1), strongly suggesting a problem with bone resorption/deposition. She is now beginning to take generous supplements of calcium and vitamin C, and has plenty of sun exposure in the summer months. Her problem appears to be a special case of a growth problem—her stature is normal—in which a laboratory test was the first clue. Upon physical examination, she has a positive Chvostek's sign and hyperreflexia, and in response to questioning she and her mother agree that she is irritable. A supplement of vitamin D and the more abundant sun of the coming summer may put things right.

However, I wasn't looking for problems with bone growth, as the proline indicates. Surprised and made wary by the inconsistency of clinical and lab data, and awakened by her autism to the possibility of a problem in her sulfur system, I took more careful notice of her other lab data. Her urine homocysteine was <1 mmol/24 hr (normal up to 4) and her serum homocysteine was low at 4.2 mmol/L. This caught my eye because recent data cited above show low homocysteine in autistic children. Her urinary cystine (20 mmol/24 hr) and her urinary cystathionine (11 mmol/24 hr) were both in the low range.

Homocysteine is like the hot ingot in our metabolic foundry, where it must be used immediately or recycled to methionine. Otherwise, its accumulation produces damage, as a sort of "promiscuous detoxification" in which normal tissues are subjected to superfluous sulfation.[4] The consequences of low homocysteine are not as well recognized. Homocysteine is the unique gateway through which thiol synthesis passes. In autistic children, this shows up in low levels of downstream metabolites—cysteine and glutathione; hence the potential for a deficit in all functions involving thiols, including detoxification and the adhesive forces that shape enzymes as well as simply hold things together at the molecular level. In other words, emerging knowledge of an integrated pathology of thiols and sulfation in autistic children leads my thinking about Sara's synthetic problem past the usual formulation of her high proline as the sole key to inefficient bone remodeling (resulting only from a lack of calcium, ascorbic acid, or vitamin D).

The reactivity (easy oxidation) of thiols that provides them with the stickiness associated with shaping proteins and binding toxins is a double-edged sword—the activity makes this chemistry particularly vulnerable to oxidative damage, especially by heavy metals. A molecule that "captures" heavy metals does not have a bright future, except as a martyr for the cause of keeping its organism clean. The autism epidemic appears to be, in part, an expression of oxidative damage within the sulfur system, related to mercury and other environmental toxins. The dynamics of the interaction between mercury and the thiols is a vicious cycle that may be initiated by damage to methionine synthase (MS) by mercury-containing compounds. The compound, Thimerosal, for example, inhibits MS at levels corresponding to about 1/100 of that found in the blood of infants, two weeks following a routine immunization containing Thimerosal.[5] It seems unlikely that the impact of mercury, and other toxins which are sufficient to produce an epidemic of autism, has sharp edges defining that impact exclusively within the population of children for which the concept of "regressive autism" is defined.

The autism epidemic is an international tragedy that is still denied by many, and subject to the perverse neglect of the guardians of public health who fund flawed epidemiological studies and ignore persuasive biologic evidence pointing to the underlying causes. That same biological evidence should catch the eye of clinicians who need not wait for the ending of debates over public policy. They should consider whether some of their patients express abnormalities that reflect changes in their sulfur systems, similar to those of our autistic children. Those changes fall into two categories: one is laboratory

evidence consistent with heavy-metal toxicity and oxidative damage (which impacts thiol chemistry with low levels of homocysteine, cyst(e)ine, cystathioinine, and glutathione), as well as abnormalities of plasma and urine sulfate. The other is clinical responsiveness to agents that may support that chemistry, such as methylcobalamin, n-acetyl cysteine, reduced glutathione, and magnesium sulfate (in the form of Epsom salts baths and natural and synthetic chelators).

Forty years ago, I graduated from Yale Medical School believing my professors' dictum that autism was the consequence of cold mothering. I also believed that autism was a "disease entity" that fit neatly into its own diagnostic circle and, as such, was isolated from all the other circles that embraced the diagnostic concepts we form about groups of people with similar pathologies. Today, I see all these circles as spheres overlapping in a vast multidimensional Venn diagram, in which their interconnections come from the logic of physiology and systems theory, with their integrative—as opposed to linear—concepts of causality. The pathophysiology of autism shares features not only with individuals with similar behavioral, cognitive, socialization, sensory, immunologic, and gastrointestinal problems, but with patients who give the appearance of having what would be considered entirely different conditions when considered within contemporary systems of classification. Even if you, your family, or your neighbors are not touched by autism, its environmental causes are likely to be nearby and expressing themselves in other ways. Clinicians with this proposition in mind will be the first to see the connections.

REFERENCES

1. Owens S. In: Baker SM, Pangborn J, Deth R, Owens S, Lonsdale D, Haley B. The Chemistry of Autism (poster presented at the Autism Research Institute's Defeat Autism Now! Conference, Philadelphia, PA, May 2003, revised 2004). Diagram and accompanying text by J. Panborn, PhD available by email from sidneymb@aol.com.
2. James J, et al. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with Autism. Am J Clin Nutr. In press.
3. Gottschall E. Breaking the Vicious Cycle. Ontario, KOK 1C0: Kirkton Press; 2002.
4. Stamler JS, Slivka A. Biological chemistry in the vasculature and in vascular-related disease. Nutrition Reviews. 1996;54:1-30.
5. Waly M, Banerjee R, Choi SW, Mason J, Benzecry J, Powers VA, Deth RC. PI3-Kinase regulates methionine synthase: activation by IGF-1 or dopamine and inhibition by heavy metals and Thimerosal. Molecular Psychiatry. 200;9:358-370.

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