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Review

Simplifying study of fever's dramatic relief of autistic behavior

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SUMMARY

Dramatic relief of autistic behavior by infectious fever continues to tantalize parents and practitioners, yet researchers still hesitate to study its physiology/biochemistry, fearing stress and heat of brain imaging, contagion, and fever's complexity. Yet what could be more revealing than a common event that virtually 'normalizes' autistic behavior for a time? This paper proposes study of three simplified scenarios: (1) improvements appearing hours before fever, (2) return of autistic behavior soon after fever, (3) improvements persisting long after fever. Each scenario limits some risk – and some explanation – inviting triangulation of decisive factor(s) in relief and recurrence. Return of autistic behavior after fever may be most revealing. The complex mechanisms that generated fever have all abated; simpler cooling mechanisms prevail – how many plausible explanations can there be? The decisive factor in fever's benefit is concluded to be water drawn/carried from brain myelin and astrocytes by osmolytes glutamine and taurine released from muscles and brain; the decisive factor in return of autistic behavior after fever is return of water.

I think we need to conduct research as if we know this is an emergency.

Martha Herbert 2009 [1]

Introduction: fever's dramatic relief of autistic behavior

Though there is practically no mention of the high fever/improved behavior phenomenon in the entire autism literature, every knowledgeable person – both parent and professional – I approached for information knew of it.

Sullivan 1980 [2]

Ruth Christ Sullivan first published anecdotal reports of fever's benefit in 1980 in *Parents Speak*, her column in the *Journal of Autism and Developmental Disorders* [2]. Campbell reported an outbreak of upper respiratory infection in a Bellevue Hospital nursery. Autistic children with fevers of 102–105 °F [38.8–40.5 °C] socialized with other children and adults; most improvements subsided a few days after temperatures returned to normal. Caparulo and Cohen reported stressful procedures like blood drawing also provoked brief dramatic improvements.

Cotterill described the phenomenon in 1985: "When autistics have a moderate fever, they invariably display dramatically more normal behavioural patterns, including a greater desire or ability to communicate.... The effect appears to reach a maximum for fevers in the range 1.5–2.5 °C [2.7–4.5 °F]." [3] Brown (1999) reported his personal observations: "[T]he changes that occur in these autistic children are… dramatic – more like a metamorphosis in which the autistic child suddenly becomes almost normal. These children experience increased alertness, a decrease in social isolation and self-injurious behavior, an increase in verbal behavior, and an attempt to reach out and communicate with adults." [4].

These reports inspired a prospective study by Curran and colleagues, who compared behavior of children with autistic disorders (ASD) during fevers greater than 100.4 °F (38 °C) against behavior of ASD children with no fever [5]. More than half the parents already knew fever helped. Parents observed less irritability, hyperactivity, repetitive acts, and inappropriate speech during fever, which did not depend on lethargy, height of fever, nor severity of illness.

Publication of this study evoked a spontaneous outpouring of parents' reports of relief by fever in autism and other disorders. Three autistic children improved briefly from a sauna, steam room, or hot tub/bath; some improved hours *before* fever's onset [6]. Zimmerman summarized parents' reports of improvements before

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fever (personal communication 2014): "My impression has been that those children who improve before the appearance of fever are those who also have the most striking improvements overall during fever (and are more likely to have enduring effects after fever subsides), possibly 10% of those who have the 'fever effect.'" Zimmerman suggested low-grade fever might explain early benefits: "It is usually a period of hours [up to 6–8] when benefits are seen before fever is recognized." He noted 80% of parents in Curran et al. [5] reported their child improved during fever on one or more *Autism Behavior Checklist* categories: "In clinical care, approximately 30% of parents report that their children with ASD improved dramatically during fever… their symptoms are so obvious the family recognize them immediately."

Informal parent surveys by the *Simons Foundation* concluded fever helps 30–40% of ASD children [7]. Their workshop on fever in autism considered the effect of temperature to increase *brain blood flow* – consistently low in these children [8] – but the usual lack of benefit of a sauna or hot tub argued against it (J Miles, personal communication 2010). One explanation may be Kiyatkin's observation that fever increases human brain temperature much more than ambient heat, especially in children (personal communication 2010).

Herbert and colleagues have been outspoken advocates of the significance of fever's benefit in papers e.g. [9], chapters e.g. [8], letters e.g. [10], and a book describing a child whose improved speech persisted *weeks* after fever subsided [11]. Herbert concluded the fever phenomenon reveals autism is a "*chronic dynamic encephalopathy*" [8] – ongoing active *reversible* brain pathophysiology.

What happens during fever?

Neurons require several orders of magnitude more metabolic energy than other cells, generating considerable heat [12]. Heat accelerates metabolism about 11% for each °C [13], so the hypothalamus regulates body/brain temperatures closely – normally 98.0–98.8 °F (36.6–37.1 °C) orally [14] – activating and integrating independent heating and cooling mechanisms to stabilize temperature at the most appropriate *set point*. When bacterial or viral infection requires the hypothalamus to raise body temperature to a new set point called *fever*, cooling mechanisms of *vasodilation* and *sweating* are suppressed. When fever *plateaus* at the new set point, skin blood flow returns to balance heat gain and loss, and the child feels neither hot nor cold [15]. When fever *breaks* (*crisis* or *flush*) skin blood vessels dilate abruptly and sweating is profuse.

Fever resembles the body's response to *cold* [16] – skin blood vessels constrict to conserve heat, and heat is generated by muscle contractions (*shivering*) and acceleration of metabolism. *Metabolic* (nonshivering) *thermogenesis* during cold is stimulated by the sympathetic nervous system (SNS) transmitter *norepinephrine* [17]. Fever's thermogenesis is largely due to *epinephrine* from the adrenal medulla, which accelerates metabolism 5–10× more than norepinephrine by stimulating SNS *β-receptors* and mobilizing metabolic fuels [14].

Current views of fever implicate environmental *pyrogens* like bacteria activating the immune system, which orchestrates the response to infection via signaling proteins (*cytokines*, e.g. *interleukins*) and hormone-like fatty acids (*prostaglandins*) that also generate heat [18]. Tang and Kiyatkin found intravenous injection of bacterial tissue in rats caused brain temperature to rise in phases. The first phase was initiated by heat conservation and production in the periphery with sustained vasoconstriction within about 40 min; about an hour later brain temperature rose again, suggesting "metabolic brain activation and subsequent involvement of central mechanisms that increase body metabolism." [18] Presumably SNS release of epinephrine.

These catecholamines also accelerate metabolism during *stress*, generating *stress fever*. Stress fever is genuine fever – body temperature reset to a higher *set point* [19]. Ordinary stress aggravates autistic behavior, but severe stress (e.g. *panic*) often relieves it briefly [2,6,9]. Kiyatkin: "[F]luctuations [in brain temperature] due to stress, environmental warming, etc. are relatively weak (up to 1.0–1.5 °C), but during fever this increase is much larger, especially in children." (personal communication 2010).

What happens hours *before* fever?

Wannemacher and colleagues investigated the response to infection in healthy volunteers inoculated with *sand fly virus* to induce mild illness [20]. Fever appeared 56–70 hr after inoculation. Hours *before* fever's onset, most plasma amino acids (AA) fell: "[S]ignificant depression in the concentration of total amino acids [and most individual amino acids] was evident 9–23 hr before the onset of fever or symptoms of illness ...." Wannemacher [21] concluded amino acids [mostly *glutamine*] released from skeletal muscles by catabolism of their proteins were taken up avidly for anabolic responses to infection by immune cells, liver, and brain.

Muscles release their *free* amino acids, however, long before their proteins break down from fever. Shabert and Wilmore [22] cited evidence adrenal glucocorticoids responding to infection or injury stimulate release of 3–4x usual amounts of glutamine from muscles – "probably all free glutamine" Wilmore observed (personal communication 2014). Shabert and Wilmore: "In the skeletal muscle-free amino acid pool, glutamine and taurine are the most abundant amino acids ...."

Glutamine released by muscles serves as provisional fuel during the loss of appetite (*anorexia*) that accompanies fever. Glutamine is alternative fuel in brain neurons and astrocytes, especially during hypoglycemia [23], primary fuel in rapidly replicating cells – e.g. enterocytes [24] and blood vessel endothelial cells – and precursor (via *citrulline*) of *arginine*, only substrate for primary vasodilator *nitric oxide*.

Glutamine in autistic disorders

Glutamine is normally the most abundant amino acid in blood, but is consistently low in plasma of ASD children, and often low in their brain [25]. Children with high brain glutamine from *urea cycle disorders* rarely show autistic behavior [26]. *Autism Research Institute* (ARI) practitioners commonly give ASD children and adults oral glutamine to heal their intestines – from 250 mg to 8 g/day – but only two of ten reported improved behavior (personal communications 2013). Verzella (MD) gives 5–7 g/day of glutamine after cleansing their intestines of pathogens like *bacteria* and *yeast*: "Multifactorial and multisystemic is the condition, so that the improvement has different aspects in different children. Most common: sedation, less stereotypies, better sleep, more concentration.... A remedy, not a cure." Some practitioners reported increased excitability from glutamine in a few children (one reported *seizures*) – probably because glutamine readily decomposes to glutamate and ammonia in the intestines. Oral glutamine may be more stable as the dipeptide *glutamine/alanine* (e.g. *Sustamine*). Branched-chain AAs are good glutamine precursors.

Taurine in autistic disorders

Pangborn found taurine was the amino acid most wasted or depleted in urine of autistic children [27]. He concluded taurine was the first (and safest) amino acid to supplement in these children, in light of the large amount of taurine in the normal fetal brain, and in breast milk, and taurine's help detoxifying *ammonia* to

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