

Did Acetaminophen Provoke the Autism Epidemic?

Peter Good

Abstract

Schultz et al (2008) raised the question whether regression into autism is triggered, not by the measles-mumps-rubella (MMR) vaccine, but by acetaminophen (Tylenol®) given for its fever and pain. Considerable evidence supports this contention, most notably the exponential rise in the incidence of autism since 1980, when acetaminophen began to replace aspirin for infants and young children. The impetus for this shift – a Centers for Disease Control and Prevention warning that aspirin was associated with Reye's syndrome – has since been compellingly debunked. If aspirin is not to be feared as a cause of Reye's syndrome, and acetaminophen is to be feared as a cause of autism, can the autism epidemic be reversed by replacing acetaminophen with aspirin or other remedies? (*Altern Med Rev* 2009;14(4):364-372)

Introduction

In the May 2008 issue of the journal *Autism*, Schultz et al reported an association between autism and acetaminophen (paracetamol, Tylenol®) given children for fever, pain, and other adverse reactions to the measles-mumps-rubella (MMR) vaccine, usually administered between 12 and 15 months of age. Children given acetaminophen after the MMR vaccine were significantly more likely to become autistic than children given ibuprofen.¹

Although distribution studies detected no association, the MMR vaccine has long been suspected of provoking autism, especially by parents whose seemingly normal child regressed into autism not long after receiving the vaccine.²⁻⁴ Schultz et al, however, raised the intriguing question whether the trigger for autism is

not the MMR vaccine, but acetaminophen given for its subsequent fever and pain. An online survey of parents yielded 83 children with autism and 80 control children ages 1-18 years. Children with autism had more adverse reactions to the MMR vaccine and were more likely to have been given acetaminophen than ibuprofen for those reactions. Compared to controls, children ages 1-5 years with autism were eight times more likely to have gotten sick after the MMR vaccine, and were six times more likely to have taken acetaminophen. Children with autism who regressed in development were four times more likely to have taken acetaminophen after the vaccine. Illnesses concurrent with the MMR vaccine were nine times more likely in autistic children when all cases were considered, and 17 times more likely after limiting cases to children who regressed.¹

Interestingly, no parent in the survey reported giving aspirin after a child's MMR vaccination. This may reflect awareness that aspirin is no longer considered safe for infants and young children, after being implicated in Reye's syndrome (liver and brain damage after viral infection) in the 1980s. Because Reye's syndrome virtually disappeared worldwide after aspirin was replaced by other antipyretics and analgesics during the 1980s, parents, pediatricians, and hospitals today commonly give infants and young children acetaminophen or ibuprofen for fever and pain.

Orlowski et al offered compelling arguments, however, that aspirin was not the cause of Reye's syndrome. Although salicylates like aspirin have been used to alleviate fever and pain since the beginning of the 20th century, Reye's syndrome was not reported until the early 1950s. Furthermore, Reye's syndrome disappeared from countries like Australia that had not given aspirin to children since the 1950s, as well as from

Peter Good – Independent researcher in central Oregon. After 30 years studying multiple sclerosis he was struck by similarities between MS and autism.
Email: petergood1@mac.com



countries like France and Belgium that continued to give aspirin throughout the 1970s, 80s, and 90s. Closely examining U.S. Public Health Service studies between 1980 and 1987 that associated aspirin with Reye's syndrome, Orlowski et al found serious problems in all – even doubt that the researchers were actually studying Reye's. They noted other studies worldwide that showed no association between aspirin and Reye's syndrome. As for the argument that Reye's disappeared after aspirin use declined in infants and young children, Orlowski et al showed that the incidence of Reye's syndrome was already falling by 1979.⁵

Synchronicity of Acetaminophen and the Autism Epidemic

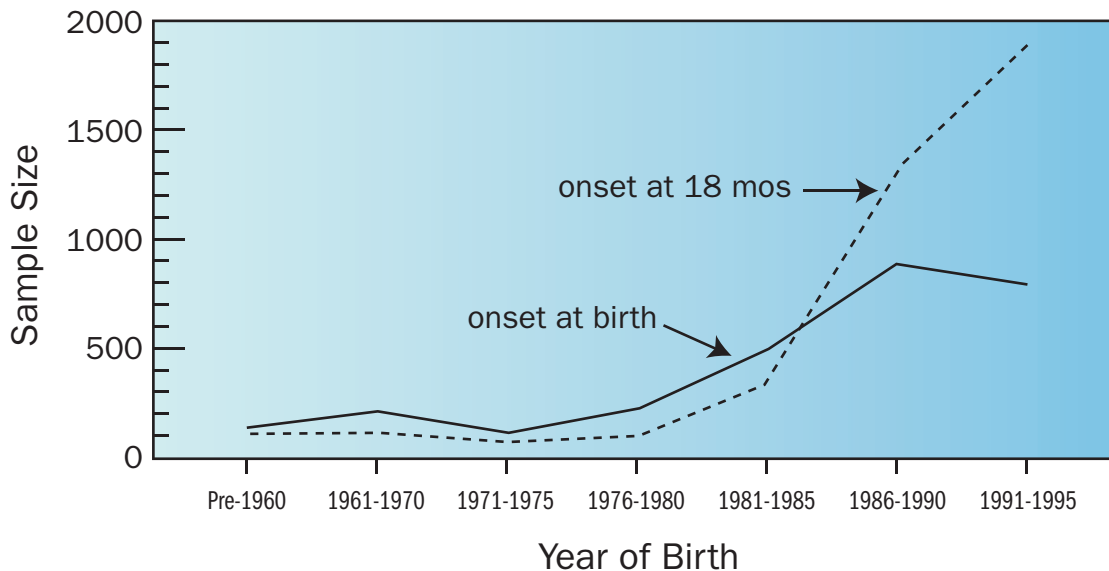
The most compelling evidence linking acetaminophen use and autism is their rapid synchronous rise in recent decades. "The incidence of autism has risen 10-fold since the early 1980s," Previc concluded, "with most of this rise not explainable by changing diagnostic criteria."⁶ Until about 1980, approximately 50-60

percent of autistic children were abnormal from birth, and 40-50 percent regressed into autism at approximately 18 months.⁴

"Around 1980," Pangborn stated, "all this began to change. The total frequency of occurrence doubled, doubled again, and by 1995 was approximately 10 times that of 1980. Furthermore, while the onset-at-birth type had increased 3 to 4 times, the onset-at-18-months type had skyrocketed to considerably more than 10 times its 1980 level." Pangborn concluded that most of the autistic population now appeared to have "an acquired disease caused by something that we were not doing 20 years ago."⁴

Pangborn's conclusions were based on thousands of cases collected by the Autism Research Institute (ARI) since the 1960s (Figure 1).²⁻⁴ When Rimland founded the ARI in 1967, parents were already reporting that their child deteriorated into autism soon after the diphtheria, pertussis, tetanus (DPT) vaccine.^{2,3} Rimland suspected the increase in autistic regression at 18 months was due to wider use of the

Figure 1. Incidence of Autism Types



From: Pangborn JB. Introduction to the diseases of autism and laboratory testing options. In: Pangborn JB, Baker SM. *Biomedical Assessment Options for Children with Autism and Related Problems*. San Diego, CA: Autism Research Institute;2002. Used with permission.



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MMR vaccine – part of an accelerated effort to eradicate measles that began in 1978.⁷ On the other hand, the 1980s was also the decade when acetaminophen largely replaced aspirin for infants and young children. In 1980, studies under the auspices of the U.S. Public Health Service and its Centers for Disease Control and Prevention (CDC) reported that aspirin was associated with *Reye's syndrome*⁸ – a rare but often fatal disease in young children after a bout of flu or chicken pox. The impact of these studies on the public's perception of aspirin for children was dramatic⁹ – perhaps abetted by the makers and vendors of acetaminophen.¹⁰ Arrow-smith et al compared nationwide sales of aspirin and acetaminophen during that time, finding sharp decreases in the purchase and use of children's aspirin between 1980 and 1985 and a reciprocal increase in sales of children's acetaminophen products.¹¹

Schultz compared the nationwide shift from aspirin to acetaminophen against the number of children with autistic disorders eligible for services in California born before and after 1980. Decreased nationwide sales of children's aspirin and increased sales of children's acetaminophen products beginning about 1980 were associated with an increased number of California children with autistic disorders born after 1980. Schultz also found that certain critical events in the history of acetaminophen use were soon followed by inflections in autism rates. In 1977 the Food and Drug Administration warned that acetaminophen could damage the liver. California children born in 1977 were less likely to be diagnosed with autism than children born in previous years. In autumn of 1982 seven people died after ingesting Tylenol capsules laced with cyanide; in 1986 one person died after ingesting Tylenol capsules similarly tampered with. These events precipitated sharp declines in nationwide sales of acetaminophen, accompanied by declines in the numbers of California children with autistic disorders born in 1984 and 1987 (Figure 2).¹²

Schultz adapted his graph from a 1999 graph by California's Department of Developmental Services (DDS), which depicted a steep rise in the number of California children with autistic disorders born after 1980.¹³ The 2003 update to the 1999 DDS report stated without equivocation: "The 1999 Report documented that beginning in the early 1980s California began to see an increasing and dramatic rise in the number of persons with ASD [autistic spectrum disorders]."¹⁴

The 1999 DDS graph looks remarkably similar to Rimland's graph of autism incidence (Figure 1) based on thousands of cases collected by the ARI.²⁻⁴ A graph in the 2003 DDS update depicting prevalence rates instead of incidence confirms that autistic disorders began to increase dramatically in California children born during the 1980s.

Toxicity of Acetaminophen

Because infant's Tylenol is three times more concentrated than children's Tylenol,¹⁵ and parents may not realize children's cold remedies often contain acetaminophen, acetaminophen overdose in young children is not uncommon.^{16,17} Schultz et al noted that sulfation by the liver is the primary pathway to detoxify and excrete acetaminophen in children younger than 10.¹ When sulfation is impaired, acetaminophen oxidizes to the toxic metabolite N-acetyl-p-benzoquinone imine, which is then detoxified by glutathione.¹⁸ Acetaminophen overdose depletes the liver's supplies of sulfate and glutathione, impairing its ability to detoxify and excrete harmful substances.¹⁹ The American Academy of Pediatrics warned that clinical signs of liver disease – fever and abdominal pain – are often treated with acetaminophen. Many cases of severe liver poisoning in children have been attributed to cumulative toxicity from repeated therapeutic doses of acetaminophen rather than acute toxicity from a single massive overdose.¹⁶ Furthermore, evidence indicates that acetaminophen, although an effective analgesic, does not reduce fever significantly.²⁰

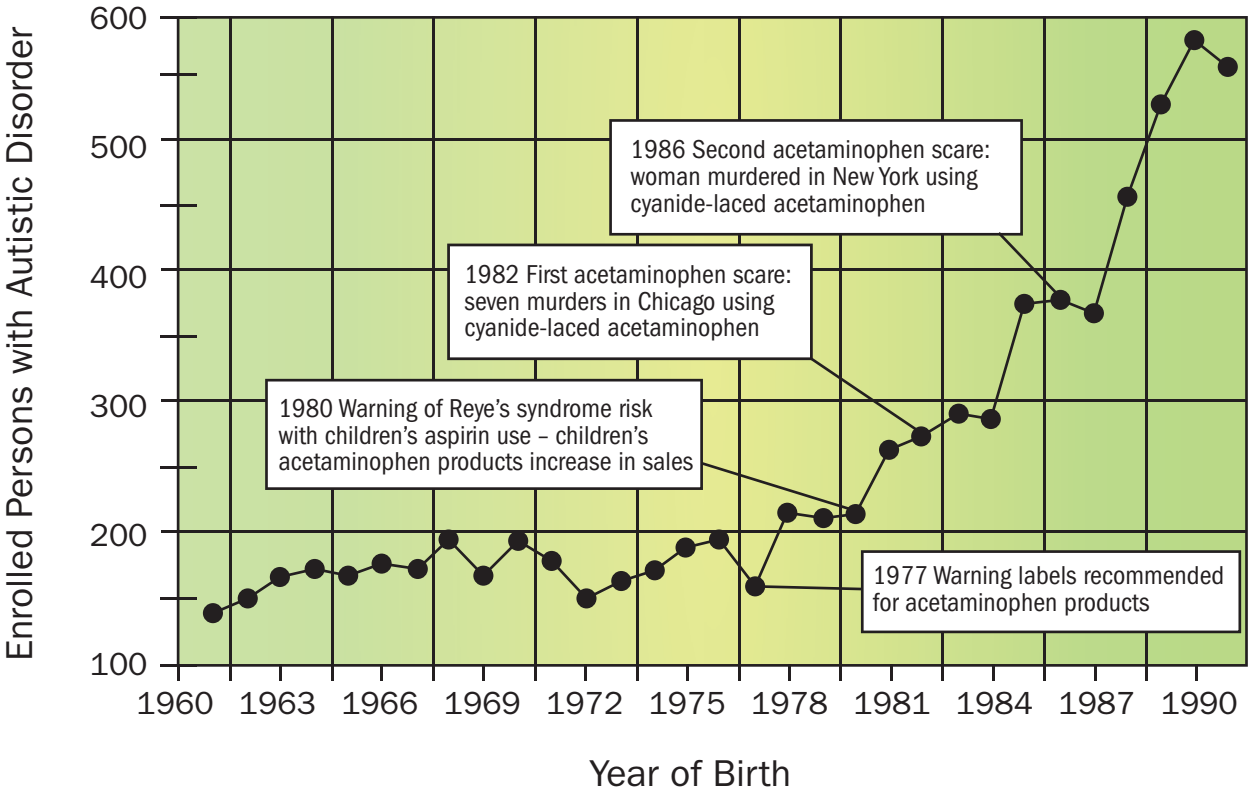
Abnormal Sulfate Metabolism in Children with Autism

Parents and autism support groups commonly report that autistic episodes are triggered when these children eat wheat, corn, sugar, apples, bananas, chocolate, cheese, and other dairy products.²¹ Because many of these "trigger" foods are high in phenolic amines (e.g., dopamine and serotonin) that depend on sulfate for excretion,¹⁹ Waring et al studied sulfate metabolism in children with autism. The liver uses sulfate derived from the amino acid cysteine to make a variety of foreign and domestic substances soluble for excretion.¹⁹ The liver also uses cysteine to synthesize the antitoxin and antioxidant glutathione,²² as well as metallothionein,



Acetaminophen/Autism

Figure 2. Number of Enrolled Persons with Autistic Disorder in California by Year of Birth and Significant Events in the History of Acetaminophen Use



From: Schultz ST. *National Acetaminophen Sales and Autistic Disorder in California*.¹² Adapted by Schultz from: Changes in the population of persons with autism and pervasive developmental disorders in California's developmental services system: 1987 through 1998. A report to the legislature (California Department of Developmental Services, 1999). Used with permission.

which transports zinc and copper and binds mercury and other toxic metals.²³ Liver detoxification is almost universally impaired in children with autism.¹⁹

O'Reilly and Waring studied 40 autistic children intolerant of certain foods and chemicals. All had very low levels of phenolsulfotransferase (PST), an enzyme that sulfates phenols and amines for excretion. To probe the sulfation pathway they administered 500 mg acetaminophen to these children, then collected urine over the next eight hours. Most children had reduced urine output over the eight hours and were feverish and

“generally off-colour.” The researchers warned about this effect of acetaminophen in these children, given relatively freely for minor illness.²⁴

Alberti et al subsequently used acetaminophen to probe the relative contributions of the sulfate and glucuronide pathways of excretion in low-functioning children with autism. They too found these children were less able than normal children to sulfate phenols and amines, and suggested this might lead to accumulations of unmetabolized catecholamine neurotransmitters (dopamine, norepinephrine, and epinephrine) in the brain, with neurotoxic effects.²¹



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Kidd concluded that these studies by Waring et al amount to “direct proof” that children with autism are less able to sulfate foreign and native phenols and amines.¹⁹

Pangborn measured plasma amino acids in 32 children with autism, detecting marginal to subnormal levels of cystine (two cysteine molecules linked by sulfhydryl groups) in 60 percent. Hundreds of follow-up analyses found cystine/cysteine levels low in autistic children 1-5 years old, although older children often had normal or even high levels. Pangborn noted, however, that Waring found higher than normal levels of plasma cysteine in children with autism, as well as higher ratios of cysteine to sulfate (suggesting a cysteine utilization disorder), and after administering paracetamol (acetaminophen), lower than normal levels of paracetamol sulfate. Pangborn also suggested that vitamin B₆/magnesium supplements may benefit autistic children partly because the bioactive form of B₆ (pyridoxal 5'-phosphate) is necessary for the conversion of methionine to cysteine.⁴ James et al detected significantly reduced plasma levels of methionine, cysteine, and glutathione and reduced methylation capacity in 80 children with autism; plasma cysteine was severely reduced in more than 65 percent.²⁵

Sulfation and Acetaminophen in Mothers of Autistic Children

One critical sulfation reaction during pregnancy converts the adrenal androgen and estrogen precursor dehydroepiandrosterone (DHEA) to its sulfate DHEAS, a storage or reservoir form of DHEA²⁶ that takes 15 times longer to clear from the blood.²⁷ DHEAS from the fetal adrenal cortex is the most common precursor of the placental estrogens so vital to fetal growth and maturation.²⁸ Geier and Geier found that children with autistic spectrum disorders had higher levels of serum/plasma DHEA and testosterone, and lower levels of methionine, cysteine, glutathione, and other cysteine metabolites. They noted that DHEA can convert to androstenedione and then testosterone, or be sulfated to the “normally favored storage molecule” DHEAS. Because sulfation of DHEA requires glutathione as a cofactor, they proposed that glutathione deficiency in these children causes less DHEA to convert to DHEAS and more to androstenedione and testosterone.²⁹ A similar shift of adrenal steroid synthesis

occurs in mother and fetus during complications of pregnancy, and in adults under stress, increasing cortisol at the expense of DHEAS.³⁰ Strous et al found plasma DHEAS significantly low in adults with autistic spectrum disorders.³¹ Croonenberghs et al detected a high ratio of plasma cortisol to DHEAS in autistic adolescents.³² Sulfation is also important for the excretion of steroids, including DHEA and testosterone.^{4,19}

Mothers of autistic children commonly suffer more bacterial and viral infections³³ and fevers⁶ during pregnancy, for which they commonly take acetaminophen.³⁴ If their babies are born cysteine-deficient, newborn boys may be more vulnerable because their uptake of cysteine takes longer to mature.³⁵ Acetaminophen given infants before the MMR vaccine may also set the stage for autism, notably when given for reactions to the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine at ages two, four, and six months – a vaccine “with the most fever/pain.”³⁶

Acetaminophen impairing sulfation before and after birth may explain why children with autism have smaller brains at birth (estrogen deficiency), then an accelerated and prolonged growth spurt of male-specific brain structures within a few months of birth (androgen excess).^{37,38} The testosterone-dependent amygdalae are larger than normal in these children and the estrogen-dependent corpus callosum disproportionately smaller.^{38,39} These anomalous brain structures in autism, and the characteristic personality, behavior, and aptitudes they beget, have been termed the “extreme male brain” by Baron-Cohen et al.³⁸ Impaired sulfation of DHEA to DHEAS before and after birth, reducing estrogens and increasing testosterone, together with impaired sulfation/excretion of testosterone, may explain these anomalies.

Current Potential Remedies

Because these children lack capacity to metabolize and excrete foreign and native toxins of all kinds, the most effective general countermeasure may be to increase their sulfur substrate, e.g., via magnesium sulfate (Epsom salts) in bathwater and/or careful doses in orange juice. Oral magnesium sulfate, which is poorly absorbed, draws water into the intestines, potentially causing diarrhea; whereas, well-absorbed magnesium taurate provides magnesium as well as sulfur from taurine.⁴⁰ Almost half of autistic children and adults benefit

when given oral vitamin B₆ plus magnesium (optimal daily dose on average: 8 mg vitamin B₆/lb body weight plus 4 mg magnesium/lb).⁴¹

Other good sources of sulfur are cabbage, onions, garlic, dried fruit,⁴² oral supplements like whey protein²³ and methylsulfonylmethane (MSM),⁴³ and a high-protein diet. Cysteine supplements, however, appear unsafe. Quig noted that high doses of cysteine (e.g., 500 mg 3 times daily) may transport mercury into the brain.²³ Pangborn warned that a sudden influx of cysteine may mobilize toxins the body is not ready or able to excrete.⁴ When acetaminophen overdose depletes the liver's supplies of sulfate and glutathione and toxicity develops, the current treatment is N-acetylcysteine to replenish intracellular glutathione.⁴⁴ Kidd concluded that N-acetylcysteine and oral glutathione were safer than oral cysteine, and noted that ascorbate (vitamin C) may protect against glutathione depletion.²² Because molybdenum supplements improved behavior in 14 of 38 autistic children,⁴² further investigations seem warranted. Torres recommended that fever suppressants be reserved for severe fevers in young children, on grounds that fever helps mature the immune system.³⁴ Large trials have shown that low-dose aspirin during pregnancy is relatively safe for mother and child.⁴⁵

Giving aspirin to children with autism, however, may tax the liver as much as acetaminophen, although salicylates are usually metabolized as glucuronides.⁴⁶ Alberti et al noted that salicylates are primary biochemical offenders in autistic children, and high-dose aspirin inhibits the sulfating enzyme PST.²¹ The Feingold Association has received parent reports of significant improvements in behavior of autistic children after removing gluten (wheat) and casein (dairy) products from their diets, as well as salicylates naturally present in fruits and vegetables. Director Hersey concluded: "I cannot say if aspirin causes more problems than acetaminophen for autistic kids. The reason why we suggest acetaminophen in place of aspirin is because aspirin is a 'salicylate' and a known troublemaker for many people. . . . Many of our members use various homeopathic remedies – they're a very good option since they don't contain unwanted additives such as artificial dyes and flavorings. Another choice would be to ask a compounding pharmacist to make up a product to fit the child's needs. . . . For a child with autism . . . it might be wise to stay off salicylates for a longer period of time since these kids are likely to be very sensitive."⁴⁷

Contrary Arguments

1. Cox and McDowell challenged the methods Schultz et al used to gather participants and controls for the online survey, arguing they were biased and insufficiently random, and no estimate of sample size was given. These writers also suspected that parents might not accurately recall years after the MMR vaccine whether their child was given acetaminophen.⁴⁸ Schultz replied that asking parents of autistic children to have their friends with normal children take the survey was an excellent way to select controls, because they represented the population studied, yet did not have autism. The original paper by Schultz et al pointed out several reasons the population of autistic children in the survey might not have been random.¹ Schultz's reply also noted that the effects of acetaminophen were so great they were significant even for the relatively small sample. To minimize recall bias they had analyzed a smaller group of children ages 1-5 years, thinking that parents of younger children would better remember whether their child was given acetaminophen after the MMR vaccine. The association of autism with acetaminophen was highly significant even for this smaller group.⁴⁹

2. Could the epidemic of autistic regression be due to factors in the MMR vaccine itself (e.g., its attenuated live viruses), which came into wider use in 1978 in an effort to eradicate measles? Dales et al calculated that the incidence of autism in California children born from 1980 onward increased more rapidly than the use of the MMR vaccine.⁵⁰ Rimland noted that the DPT vaccine also provoked autistic regression.^{2,3} In any case, greater use of the MMR vaccine does not explain three times more cases of autism present at birth. The mercury-containing preservative thimerosal in vaccines also depletes glutathione,⁵¹ but thimerosal was never a component of the MMR vaccine.⁵² Furthermore, the incidence of autism continues to rise even though thimerosal is no longer used to preserve most pediatric vaccines.⁵³ On the other hand, in some states children still receive thimerosal-preserved vaccines.⁵⁴ Haley also noted that the oxidation of sulfite to sulfate requires a molybdenum cofactor inhibited by mercury.⁵⁴ Urinary sulfite is high in autistic children, and molybdenum supplements improved clinical symptoms.⁴²

3. If replacing aspirin with acetaminophen provoked the autism epidemic, why is its prevalence in the United States comparable to its prevalence in France,⁵⁵

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where children continued to receive aspirin throughout the Reye's epidemic? Deligne et al reported that in 2003, 90 percent of more than 500,000 prescriptions for fever in French infants less than three months old were written for paracetamol (acetaminophen).⁵⁶

4. If the MMR vaccine is usually given at 12-15 months, why does autistic regression usually occur at about 18 months? Schultz pointed out that regression often develops gradually, over a period of months. Acetaminophen given for the vaccine, he suggests, may weaken a child's immune system, so the child gets sick again and takes more acetaminophen, thus "slowly regressing into autism."⁵⁷ This scenario may also apply to acetaminophen poisoning the liver. By depleting sulfate, glutathione, and metallothionein, acetaminophen may make a child more vulnerable to a variety of substances, even the phenolic amines and salicylates in food. Reddening of the face and ears (a common response to trigger foods) may be mistaken for fever, prompting more acetaminophen, which eventually reaches toxic levels. Fever and abdominal pain from unsuspected liver damage are commonly treated with acetaminophen.¹⁶

Testing the Hypothesis

Levels of cystine/cysteine in hair or blood may reveal the extent of depletion after acetaminophen. Yet can it be ethical to administer acetaminophen to a child whose ability to detoxify acetaminophen may be critically impaired? One alternative: when parents become sufficiently wary of giving acetaminophen to infants and young children, the same kind of "natural study" may occur as when acetaminophen replaced aspirin in the 1980s.⁹ When enough parents stop giving (and taking) acetaminophen, and give aspirin or another remedy instead, any effect on the incidence of autism may be apparent within several years.

Conclusions

The synchronicity Schultz detected between the onset of the autism epidemic and the surge in acetaminophen use after the CDC's 1980 warning against aspirin seems unlikely to be artifact or coincidence. The Autism Research Institute also concluded that autism rates began to multiply around 1980, especially regression after the MMR vaccine. Schultz et al found that children given acetaminophen for reactions to the MMR vaccine were more likely to become autistic than

children given ibuprofen. Because acetaminophen suppresses the immune system as well as depletes the liver's supplies of detoxifying agents, the question remains open which pathology is more decisive. Immune suppression inducing more illness thus more acetaminophen may eventually result in toxic levels. Impaired sulfation of DHEA and testosterone before and after birth may explain the extreme male brain.

For autism, the critical distinction between aspirin and acetaminophen may be the difference between aggravation and provocation. Although aspirin and other salicylates can worsen behavior in children already autistic, they have not been implicated in autistic regression in previously normal children. Acetaminophen, by contrast, has been so implicated. Acetaminophen taken during pregnancy may provoke autism present at birth; acetaminophen given after birth (e.g., for vaccine reactions) may provoke autistic regression. If aspirin is not to be feared as a cause of Reye's syndrome, and acetaminophen is to be feared as a cause of autism, the most direct countermeasure may be low-dose aspirin to relieve pain and high fever in infants and young children (and mothers during pregnancy). If acetaminophen provokes autistic regression after vaccines, parents have less reason to fear vaccines. If mercury in vaccines also provokes regression, mercury should be feared, not vaccines.

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