Response to Dr. Ari Brown and the Immunization Action Coalition

Thoughtful House
Center for Children

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Informed consent is a crucial element of the foundation upon which ethical medical practice rests. Providing patients, parents, or guardians with an honest assessment of the risks and benefits of any medical procedure requires the physician to be, to the best of his or her ability, "informed."

This document is produced by Thoughtful House Center for Children in response to one written by Dr. Ari Brown titled "Clear Answers and Smart Advice About Your Baby's Shots," which attempts to deal with the vaccine-autism controversy. Brown is an official spokesman for the American Academy of Pediatrics. Her document [1], is endorsed and published by the Immunization Action Coalition (IAC), a US organization funded by the Centers for Disease Control (CDC) and the vaccine manufacturers. In short, it is the public relations arm of those who are legally and ethically responsible for vaccine safety. Given this background, one might reasonably expect a comprehensive, well researched, and persuasive overview. Since the topic of vaccination is so important and because we have major concerns about the accuracy of much of what this document says, we are providing a point-by-point response. (Note: Dr. Brown's comments are italicized.)

"I've heard autism is on the rise. Why?"

Brown begins by addressing the rise in autism diagnoses. The question of whether the rise is real or not is an important one that has profound political and policy implications. It matters because if the increase is real, there must be an environmental contribution to the cause. There's no such thing as a purely "genetic" epidemic. If there's an environmental cause(s), then it, or they, can be found and eliminated, thereby preventing many new cases of autism. The search for an environmental cause might also inform treatment strategies for existing cases. Denial of the epidemic takes resources away from looking for an environmental cause.

Brown proposes alternative explanations for the rising number of cases: "*Displacing one diagnosis for another: In previous generations, many children were diagnosed with mental retardation, schizophrenia or some other psychiatric disorder. Today many of these same kids are diagnosed with severe autism."*

Brown's position is not supported by the scientific evidence. In 2002 a study of California children, born 1987–1994, examined the degree to which improvements in detection of autism and changes in diagnostic guidelines have contributed to the observed increase in autism prevalence [2]. The study also evaluated any change in prevalence of mental retardation (MR) without autism over the same period. The authors reported that autism prevalence increased by 9.1 per 10,000, while during the same period the prevalence of mental retardation without autism decreased by a similar amount. They initially concluded that diagnostic substitution (displacing one diagnosis for another) accounted for the observed increase in autism. The authors' conclusions were amended, however, after Blaxill, *et al.* pointed to several fundamental analytic errors, including the failure to account for age-related ascertainment biases in the mental retardation category [3]. After a re-analysis in which these factors were taken into account, Croen*, et al*. withdrew the conclusion of their original paper, stating instead that "diagnostic substitution does not appear to account for the increased trend in autism prevalence" [4].

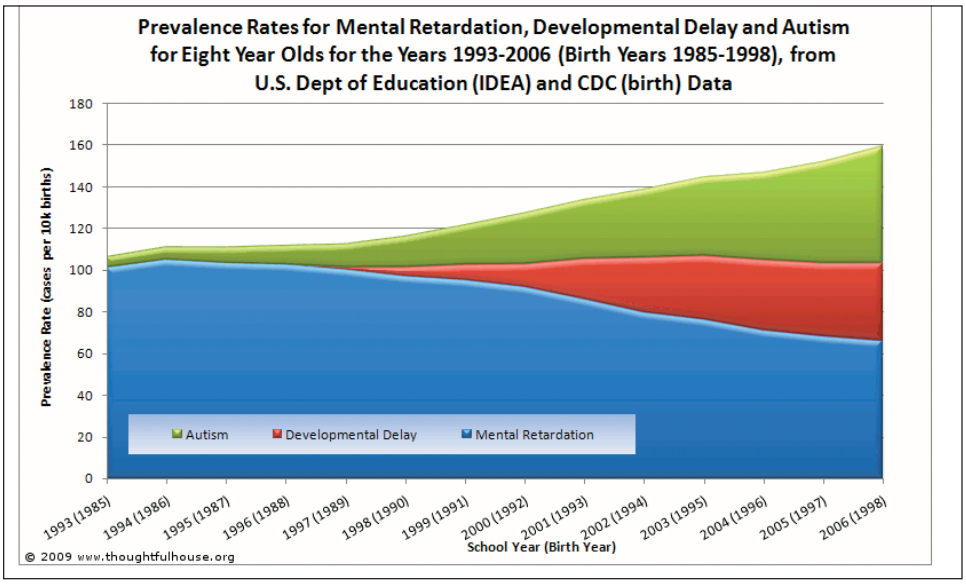
A larger study reported by Newschaffer, *et al*. also failed to find a decline in either mental retardation or speech and language disability, while autism spectrum disorders (ASDs) continued to rise [5].

Finally, in 2006 Shattuck sought to revive the hypothesis of diagnostic substitution that by then had been either proposed and retracted [2-4], disavowed [6], or falsified [7-10] in previous studies [11]. Again, it was Mark Blaxill who pointed out that in constructing a set of diagnostic categories that showed a declining trend in MR, Shattuck omitted developmental delay (DD), a category that was added to US special education in 1997 and was often used interchangeably with MR [3,10]. A simple analysis was drawn up showing the effect of adding DD cases to the data on the supposed substitution of autism for MR, which is shown on the following page. The inclusion of the DD category eliminated Shattuck's hypothesized substitution effect between MR and autism.

"Changing criteria, broader diagnosis: The definition of autism has changed over the years. The Diagnostic and Statistical Manual of Mental Disorders (DSM) is the authoritative bible for psychiatric disorders in the US. The first two editions never even listed autism as a diagnosis…it was not until 1980 when psychologists recognized autism. That's when the DSM for the first time listed criteria for diagnosis of autism. The autism diagnosis broadened again in 1994 when several more disorders were officially added to the DSM: Pervasive Developmental Disorder (PDD), PDD-NOS (not otherwise specified, Childhood Disintegrative Disorder)… By expanding the definition of autism, suddenly many more kids were declared autistic…"

This is incorrect. PDD was included in the DSM-III in 1980 [12]. PDD-NOS appeared in the DSM-III-R in 1987 [13], and Childhood Disintegrative Disorder was included in DSM-II in 1968, as a psychosis of infancy and early childhood [14]. The only addition has been the specification of Asperger's syndrome in 1994, a condition previously recognized and subsumed under DSM classifications from 1980 onwards as either Childhood Onset Pervasive Developmental Disorder, Atypical Developmental Disorder (DSM-III) or as PDD-NOS in DSM-III-R. In fact, the diagnostic criteria for autism underwent a corrective narrowing in 1994 [15], adjusting for apparent false-positives noted in DSM-III-R, and converging with ICD-10, which made the autism diagnosis more exclusive and the non-autistic spectrum disorders more clearly defined. Despite this, the dramatic increase in numbers of children with both autism and non-autistic spectrum disorders has continued.

"Unfortunately, many states don't break out where kids are on the au-



The graph shows how increased numbers in the category of developmental delay (DD) substituted for the apparent decline in mental retardation (MR), while autism numbers independently continued to rise. (Source Blaxill M and Hollenbeck D. at www.fightingautism.org/idea/autism-diagnostic-substitution.php)

tism spectrum. California's autism rate is often cited in the media as example [sic] of the 'autism epidemic'—yet California doesn't specify where kids are on the autism spectrum, so it's hard to get solid numbers."

This is also incorrect. California's autism numbers are provided by the Department of Developmental Services, based on DSM criteria. In order to be eligible for services in this system, a professional diagnosis of full-syndrome DSM autistic disorder is required. California data exclude those with Asperger's, PDD-NOS, and all other non-autistic PDD diagnoses [16].

"Better awareness, better and earlier diagnosis: When it comes to autism, this newfound awareness is actually a positive step. More people—parents and doctors alike—are on the lookout for children with autism."

Not in California. Notably, in order to reduce the growing number of new autism diagnoses, the state government, in response to the budget crisis in 2003, changed the eligibility criteria for all conditions entitled to services, to exclude children who could tie their shoelaces. Despite this effort to artificially reduce autism numbers, children with autism fail this ill-conceived test and continue to flood into the system in record numbers [16].

"Making a diagnosis and starting therapy earlier in life improves kids' long-term outcomes. But it also looks like autism is on the rise. Why? Because kids were previously diagnosed with autism after age five or six. Today, kids are diagnosed as early as 18 months of age. This adds many more kids to the rolls ... but is autism really increasing? Or is there just an earlier diagnosis?"

Earlier diagnosis has no impact on the ultimate prevalence for any particular birth cohort (group born in any calendar year). Earlier diagnosis would initially lead to an apparent increase in numbers, but this apparent increase would disappear over time as all children who were going to develop autism in any particular birth-year group were eventually diagnosed. If earlier diagnosis were the cause of the "apparent" rise, then by age ten, for example, all children with autism would be diagnosed whether they were born in 1980 or 1990. This has not happened. There were many more children with autism who were born in 1990. The California data show that when comparing the prevalence of autism by age six in 1989 with children aged six in 2000 (by that age the great majority of affected children would have been diagnosed in both years), the prevalence of autism was greater by a factor of over sevenfold in 2000 compared with 1989 [17].

Although not available to Brown at the time she went to press, a new study of autism incidence in California [18] dispels the myth that the rise isn't real. This important study, published in the January 2009 issue of the journal *Epidemiology,* was reported as indicating that "research should shift from genetics to the host of chemicals and infectious microbes in the environment that are likely at the root of changes in the neurodevelopment of California's children" [19]. "It's time to start looking for the environmental culprits responsible for the remarkable increase in the rate of autism in California," said UC Davis M.I.N.D. Institute researcher Irva Hertz-Picciotto [19], a professor of environmental and occupational health and epidemiology, and an internationally respected autism researcher.

"Why does the U.S. have so many autism cases? Autism is not just an American disease—it happens worldwide. But why do the U.S. and United Kingdom have such high autism rates? That's because the U.S. and U.K. have done the lion's share of research and studies into autism."

It is far more likely that the US and the UK have done more research because this is where the epidemic was first manifest, and where the caseload is greatest and therefore where the need for research is self-evident. Research is responsive—albeit typically belatedly so—to demand. It rarely anticipates demand, and it did not cause the rise in autism.

"And counting autistic kids is a relatively recent phenomenon. Before recent legislation led to schools labeling more kids as autistic, researchers just looked at either medical or school records to determine autism rates. This was imprecise to say the least."

Brown is wrong; pervasive developmental disorders have been the subject of empirical diagnostic trials for decades. Indeed, the changes implemented in versions of DSM from DSM-III to III-R to IV were based primarily on extensive, multisite, international field trials comparing current and proposed definitions [20, 21].

With respect to legislation for schools, children with autism have been entitled to special education benefits under the federal-state IDEA program since its inception in 1975. IDEA was amended in 1990 to require that autism be counted and reported separately because it was rising faster than all other covered disabilities [22]. The change in IDEA did not cause the epidemic—it was a logical response to it.

"Prevalence vs. Incidence: Most of what we know about autism rates is based on prevalence studies: these are a sampling of a population at one point in time used to estimate overall rates. By contrast, incidence studies identify the ACTUAL number of autism cases over a period of time."

This statement is inaccurate; a prevalence estimate is not a "rate" but a proportion (a rate is a measure of occurrence over time). We might describe prevalence as a snapshot, and incidence as a short movie. Brown contends that prevalence studies provide only estimates based on a population sample, while incidence studies (somehow) provide actual numbers of cases, rather than mere estimates. In fact, incidence is also an estimate, an approximation based on population samples. The difference is that incidence estimates involve counting the number of new cases occurring over a specified time-period (*e.g.*, the number of new flu cases per month per thousand in the population) rather than the number of existing cases at any one time (*e.g.,* all flu sufferers at a single point in time). Both are estimates, and neither is more nor less accurate than the other. They simply measure different things.

"The only way to know if autism is really an epidemic is to see a rise in the incidence of autism." Incidence studies would provide no further clues about the reasons for the rise than do prevalence studies. The reason incidence studies would advance our understanding of causality is that they would help us design studies with sufficient power to compare levels of risk between groups, e.g., the fully vaccinated vs. the never vaccinated.

"Unfortunately, there are very few incidence studies of autism. That's because it is extremely difficult to do this research. Only one incidence study on autism is available—that 2005 report found that rates of PDD in the 90's were unchanged. So even though PREVALANCE studies seem to show autism is increasing, the incidence proof is lacking."

This is incorrect. Several incidence studies are available, and they show a rise. Honda, *et al.* published a study on the cumulative incidence of autism in Yokohama, Japan. They found a remarkable rise in incidence, from less than 20 per 10,000 per year in 1987 to over 160 per 10,000 per year in 1994—just a seven-year period, which concomitantly followed the introduction of the MMR vaccine [23]. (Additional data presented in this paper have been misinterpreted as indicating no effect of MMR on rising incidence; this is discussed in detail below.)

Kaye, *et al.* carried out an incidence study of autism in the UK using the General Practitioners Research Database; they found that the incidence of newly diagnosed autism amongst children under 12 years of age increased sevenfold, from 0.3 per 10,000 people in 1988 to 21 per 10,000 people in 1999 [24]. Powell, *et al.* have provided a further incidence study from the UK [25], and now another is available from California, confirming a real and major increase [18]. For a more detailed analysis of this issue, one can read Mark Blaxill's "What's going on? The question of time trends in autism"[26].

"Social acceptance: We've come a long way since autism was first identified as a disorder. Originally, experts thought autism was caused by poor parenting—namely, the mother."

This is true; in fact, a generation or less ago, "refrigerator mothers" were blamed for hating their children and thus causing their children's autism.

"Today, we realize it is not mom's fault—and thus parents are more willing to accept an ASD diagnosis. And the diagnosis now allows for special education services, which many parents realize can help their child."

The implication that there might be a group of undiagnosed older people with autism has been used by others to argue that this has kept apparent incidence rates lower in the past. If so, where are all the autistic adults? There should be at least 1 in 150 walking around in plain view or in institutions if this suggestion is true; although studies have searched [27-29], the few cases that have been found—they have been referred to as the "Hidden Horde," somewhat ironically—could not account for the rise.

"Over or misdiagnosis? There is so much awareness now of Autism Spectrum Disorders, that perhaps clinicians are over diagnosing it. One reputable study suggests that kids who actually have anxiety disorders, obsessive-compulsive disorders, and personality disorders may be misdiagnosed now with ASD."

The "reputable study" cited by Brown makes no reference whatsoever to anxiety disorders, obsessive-compulsive disorders or personality disorders [30]. In addition, the reference she mis-cites is a theoretical analysis, and not one based upon an actual population of children. As such, it remains speculative. In contrast, a study from the M.I.N.D Institute at UC Davis showed that a comparison of diagnostic quality in two groups of children with autism—one diagnosed in the mid-80s and one diagnosed in the mid-90s—showed that the diagnostic precision was identical in both groups [31].

"These are possible explanations for the 'autism epidemic'—but we don't have all the answers yet. The bottom line: in the 1980's, one in 10,000 kids were diagnosed with autism. Today, it's one in 150. The U.S. is not the only country seeing this trend. Australia, Canada, Denmark, Finland, Iceland, Japan, and Sweden also report a disconcerting rise."

In 2009 this "1 in 150" number is likely to be considerably higher. Brown bases her statement on data from the Centers for Disease Control and Prevention (CDC). That in turn is based on data from six years ago on eight-year-old children. In fact, the CDC has two ongoing projects to study autism prevalence: ADDM Network and the MADDSP. Back in 2003 the MADDSP program published a study pegging autism prevalence at 1 in 250, based on data recorded in 1996. Four short years later, on February 9, 2007, the ADDM Network published two studies indicating autism prevalence at 1 in 150, using data from 2000 and 2002. The second of these studies showed that several states had a statistically significant growth of autism prevalence between 2000 and 2002 [32].

The CDC updated their website on February 7, 2007 stating that: "CDC will soon publish the following: An update from MADDSP on the prevalence of ASDs over time in metropolitan Atlanta and updated reports from the ADDM Network on the prevalence of ASDs in multiple areas of the United States in 2004 and 2006." It is two years later and this data has not yet been published or released.

In 1992 there were 15,580 affected children in the IDEA (public education) system; fourteen years later there were 224,594 children [33]. If the increase were due to greater awareness, as Brown contends, it would mean that as recently as 1992, health care professionals and schools were unaware of (or willfully blind to) 93% of affected children. This seems unlikely.

Bottom line: the autism epidemic is real; already, far too much precious time has been wasted instead of mobilizing the necessary scientific, medical, and educational response.

"Okay, so what causes autism? The million dollar question. There appear to be four chief suspects. One, genetics: We know genetics plays a role. Studying twins is an obvious way to detect genetic disorders. If one identical twin has autism, up to 96% of the time, so will the other twin. And siblings of ASD kids have a 5% risk of having an autistic disorder"[34].

Brown's reference [DSM-IV-TR] does not report the studies, as she implies. Nonetheless, reliance solely on historical twin studies involving children born before the upsurge in autism presents a limited and potentially misleading picture. Blaxill has reviewed and written on this issue in some detail [35]. He notes that, "Three twin studies [36], [37], [38], published in 1985, 1989 and 1995 and covering twin populations born well before the sharp autism increases of the 1990s—form the core evidence base for the claim of high identical (monozygotic [MZ]) twin concordance, with a range of 60-90% concordance." There are, however, several other studies that report lower rates. The first autism twin study, from 1977, reported identical twin concordance of only 36% [39]. Another more recent study reported identical twin concordance of 44% [40]. A recent unpublished study suggests current rates might be as low as 59% [41] If autism were entirely genetic, only individuals with specific genes would have the disorder. Concordance for autism should be high in identical compared with non-identical (di-zygotic [DZ]) twins. In other words, the more "genetic" autism is, the higher the concordance ratio (MZ:DZ) should be. Once again, Brown's numbers appear to rely on historical studies and small samples of twin pairs that might not be relevant to the current epidemic. More recent autism twin studies suggest that the MZ/DZ concordance ratio might be less than 2 [42], while the unpublished study of California twins cited above estimated the ratio to be somewhere in the range of 1.6 to 6.3 [41]. Of the California data, the authors noted, "These data suggest that heritability estimates from previous studies may have overestimated the role of genetics and underestimated the role of environmental factors in the etiology of autism" [41].

Also of relevance here is that a real change in concordance (rather than an apparent change due to previous overestimates) would indicate an increasing environmental contribution. Recent data suggest that concordance ratios are, indeed, changing and suggest a trend towards higher concordance for autism in non-identical twins. This suggests a move away from a purely genetic disorder to one determined centrally by environmental factors, though still with an important genetic susceptibility component (see Richard Lathe's *Autism, Brain and Environment* pp. 55-56 [43]). Lathe also points to a decline in relative rates of ASD associated with known genetic causes (such as Fragile X syndrome) as indicating a true rise in incidence, unrelated to specific genetic causation. A review of the literature addressing Fragile X frequency indicated a strong reduction in the proportion of ASD children with this genetic anomaly over the period 1985 to 2000 [44], and this has been confirmed by more recent studies [45]. In other words, Lathe concludes, "…a smaller proportion of total ASD children [have the Fragile X anomaly] because the number of children with ASD has risen" (pp. 57) [43].

While Brown is confident that the genetic seed will one day bear fruit, she does acknowledge that *"to date, the exact gene has not been identified…."* That is because there is no "*exact gene*." The latest results from the immense *Autism Genome Project Consortium* (AGPC) study are a testament to the frustrations of genetic research in autism [46]. Their analysis of genetic material from nearly 1,500 families with multiple affected children provided the best opportunity yet of locating areas of the parental genome that could be linked to their autistic offspring. Yet again, Blaxill has provided a careful and critical analysis of the AGPC's findings. He wrote, "The results of the AGPC effort produced a result that is little different than the result one might expect from

taking a randomized group of unaffected families. It also failed to replicate any of the most highly touted suggestive findings from earlier genome scans. The negative AGPC findings provide strong evidence that heritability claims in autism are exaggerated if not false" [35].

Perhaps unaware of the AGPC's failure, Brown continues: *"In 2008, researchers identified a specific gene in some kids with autism. This gene is involved in controlling brain cell communication [47]. It appears that some kind of mutation in this gene causes a risk of autism within families."*

The APGC findings in respect of this gene, Neurexin-1 (NRXN-1), consisted of an unusual mutation found in the gene in only two sisters out of 3,000 individuals analyzed. This finding has not been supported by the results of a more recent study [48].

"Other researchers have found abnormalities on chromosomes of autistic kids. Hence it appears that autism is caused by several different genetic defects, although researchers haven't quite figured out the puzzle yet."

"*Haven't quite,*" unfortunately means "nowhere near." While specific genetic deficiencies associated with autism are well documented, such deficiencies are rare and cannot explain more than a very small proportion of ASD cases. Other heritable (genetic and epigenetic) factors almost certainly contribute to autism, yet ten genome-wide scans have failed to identify consistent, reproducible, statistically significant genetic associations with autism. The genetics of autism has been studied extensively, at huge cost, for precious little return. The current view is that for the majority, autism is a disease involving many genes that influence susceptibility to environmental causes.

Next on Brown's list of possibile causes is: *"Abnormal brain growth: Although the cause is unknown, autistic children have problems with brain growth. Babies are born with immature brains that grow rapidly and make nerve connections called synapses ... like an information superhighway. In the normally growing brain some branches of this superhighway get 'pruned.' In the autistic child's brain, the pruning process is defective. This may explain why babies with autism have abnormally rapid head growth under one year of age. Boys with ASD seem to have higher levels of hormones (insulin-like growth factors), which may contribute to the larger head size, weight, and body mass index."*

Abnormal brain growth is not a cause of autism, but occurs in *some* children in association with their autism. Whatever causes abnormal brain growth in these children might also be a cause of their autism, but the abnormal growth itself is likely to be part of the disease process in some children, rather than a cause. While Brown has put abnormal brain growth up as a possible cause of autism in her pamphlet, she herself wrote in 2004*, "One interesting study… tied autism to abnormal head growth in infants under a year of age. <u>While this is not the cause of autism</u>* [emphasis added]*, it is hoped this discovery may lead to better diagnosis and early treatment of autism" [49].*

Next Brown raises the lid on the contents of Pandora's box: *"Environmental triggers: Is there some environmental exposure that sets off abnormal brain development in a genetically predisposed baby? Maybe. And that exposure may happen at or shortly after conception—before a mother even knows she is pregnant. There is a critical period of fetal brain development that occurs at 20-24 days after conception where the brain is most sensitive to injury. Here are just a few theories that scientists are exploring as a cause for autism: flu exposure during pregnancy, and folic acid levels in Dad-to-be's sperm (possibly a too-high level can lead to problems). Studies done by the Environmental Working Group have found about 280 environmental toxins in umbilical cord blood—could one of these be a trigger?"*

Government officials [50], including Dr. Tom Insel, Director of the National Institute of Mental Health and Chair of the Interagency Autism Coordinating Committee, and an emerging scientific consensus, agree that autism is caused by environmental triggers in children with undetermined genetic susceptibility.

There are known and widely accepted environmental causes of autism ranging from pre-birth exposure to thalidomide, the anti-seizure medication sodium valproate, and rubella virus (German measles) [51]. Postnatal exposure to neurotoxins (e.g., Phenylketonuria (PKU) [52], for which children have the heel-prick test at birth) and viral infections including rubella [53, 54], measles [55-60], and herpes viruses such as herpes simplex [61, 62], cytomegalovirus (CMV) [63-66], and Epstein-Barr virus [67] have been causally linked to autistic syndromes. Specifically, measles and measles-containing vaccines and vaccines "unspecified" have also been causally linked to childhood developmental disorders, including ASD [68-74] and developmental regression [75].

"There is also a growing body of evidence that newborns who are later diagnosed with ASD already have abnormal levels of certain proteins in their brains. So, having an environmental trigger in the womb during a critical period of brain development seems a plausible explanation for autism."

Although the "*growing body of evidence*" is unreferenced, we are assuming that Brown refers to the 2001 and 2006 studies of Karin Nelson and colleagues [76, 77]. While the data were interesting, there were marked differences between the authors' findings in the first and second studies that suggest problems with methodology, leaving the interpretation in limbo, at least for now.

"What about vaccines? There has been much talk about this theory, specifically that trace amounts of mercury used as a preservative in many vaccines prior to 2001 caused a spike in autism. We discussed this issue in depth in Baby 411, but just to sum up: the scientific evidence does not support this theory. Research during the past ten years has taken a long hard look at vaccines and found conclusive evidence that vaccine exposure is NOT the turn-on switch for autism."

Brown's claim is incorrect. Vaccines are on the table. The Institute of Medicine (IOM) hosted a two-day conference in April, 2007, "Autism and the Environment: Challenges and Opportunities for Research" [78]. The workshop discussed environmental causes, including vaccines, and suggested a long list of related research opportunities.

The history of the "*trace amounts of mercury"* theory is covered in David Kirby's excellent book *Evidence of Harm* [79]. A few facts are worth reviewing. It was Dr. Maurice Hilleman of Merck (Pharmaceutical) who drew the attention of his company's executives to safety concerns over Thimerosal, the form of mercurial used as a preservative in multidose vaccines. In a memo to his Merck colleague Dr. Gordon Douglas in March 1991, Hilleman not only reported these concerns but presented his estimate that the mercury load to a fully vaccinated US infant would be 57 times the Swedish daily allowance [80]. In the memo he bemoaned the lack of any science that identified the safety of using Thimerosal, encouraged the conduct of such science in animal models, and listed alternative and potentially safer preservatives. It appears that his warnings went unheeded. Hilleman's key document was to remain in a company "box" and was not disclosed during the process of legal discovery by lawyers representing children potentially harmed by Thimerosal-containing vaccines [81]. As attorney and board member of SafeMinds [82] Jim Moody put it, "This is the sort of thing that makes a plaintiff's lawyer salivate."

In fact it was a group of parents who recognized the possible implications of this toxic exposure in relation to their children's autism [83], and who posed the questions that the regulators had so carelessly passed over. It was at this point that Dr. Peter Patriarca, Director of the Division of Viral Products at the FDA, recognizing that no one had done the simple math to determine whether the mercury levels in the new infant vaccine regimen were actually safe or unsafe, wrote to the head of the CDC, "I am not sure if there is an easy way out of the potential perception that the FDA, CDC, and immunization policy bodies may have been 'asleep at the switch' regarding thimerosal until now" [84].

As salt to the wound, Dr. Neal Halsey, one of the architects of US vaccine policy—now seemingly awake—when asked by parent advocates at a public meeting why they would even give a newborn infant with no risk factors a vaccine for a disease predominantly of intravenous drug abusers and the sexually promiscuous (hepatitis B), answered, "Because we can" [85].

Brown seeks to offer some reassurance that the CDC giant actually sleeps with one eye open:

"The U.S. Centers for Disease Control and Prevention (CDC) has long-term studies underway to examine vaccines and autism. The most recent results, published in the New England Journal of Medicine*, showed that the mercury preservative previously present in vaccines had no significant effect on either intelligence or developmental delays in kids ages seven to ten."* This study by Thompson, *et al.* [86] is addressed later (page 6).

The IOM have based their analysis of the possible relationship between Thimerosal and autism almost exclusively on human population-based records'

studies. Despite this, there are compelling data from animal models that Thimerosal, in typical vaccine concentrations, is capable of causing significant neurotoxicity with associated behavioral and developmental abnormalities. The IOM made this same error with Gulf War Syndrome [87], thereby missing the fact that many soldiers were made ill by "protective" exposures, including vaccines. (They were rightly admonished for this error by Congress.)

Brown's final contender for autism's cause is premature birth: *"Premature birth: A recent study in the journal* Pediatrics *found that premature babies born at 25 to 26 weeks gestation have a 25% chance of developing an autism spectrum disorder."*

It is entirely possible that this is because at an earlier gestational age and often a very low birth weight, the immature immune system of premature babies is exposed to vaccines on a routine schedule that allows for no adjustment according to their low body weight and often precarious medical state. On a dose per kilogram of body weight, these children are at the greatest risk of toxicity for many reasons, not least of which is their inability to produce the mercury-binder metallothionein in the liver, and hence to excrete mercury from the body. Unfortunately, this study did not collect vaccination history information either for the mothers or for their infants.

"Is it possible that autism is really mercury poisoning?" We will now deviate from the order of Brown's text and place her own tutorial on mercury in front, in order to give context to her subsequent statements on the properties and effects of different mercury-based compounds. She provides: *"A quick chemistry lesson: certain compounds have completely different properties even though they have similar sounding names. For instance, there are TWO types of mercury: methyl mercury and ethyl mercury. The type of mercury that has raised health concerns is methyl mercury. Methyl mercury is a small molecule that can get into the brain and takes almost TWO MONTHS to break down. High concentrations of methyl mercury can be found in tuna, swordfish and shark from contaminated waters… Now, let's contrast that with ETHYL mercury, which is/was the type of mercury used in vaccine preservatives. Ethyl mercury (thimerosal is an example) is rapidly eliminated from the body within a WEEK. Compared to methyl mercury, ethyl mercury is a much larger molecule that cannot enter the brain."*

There are at least three kinds of mercury that are of concern in the current debate. Brown discusses two organic mercurials—methyl and ethyl mercury. On the matter of their chemistry, the description provided is wrong. Both methyl and ethyl mercury are very small, with respective molecular weights of 229 for ethyl mercury and 215 for methyl mercury, the size difference being one carbon atom in length, a minute difference [88]. It is likely that either kind can enter the brain attached to the amino acid cysteine and be transported by an amino acid carrier protein. The relevant literature shows that mercury from Thimerosal does indeed enter the brain [89] where it is converted to inorganic mercury—the third form—which is very hard to get rid of.

Rather than properly focusing on toxicity concerns over ethyl mercury (the form in vaccines) the text provided is confusing, as the descriptions skip between the effects of the different mercury compounds that Brown clearly sought to distinguish in her earlier chemistry lesson.

Brown's claim that "*Ethyl mercury is rapidly eliminated from the body within a WEEK"* is also incorrect. It is not appropriate to assume that removal of mercury from the blood, as measured in the study of Pichichero, *et al*. [90] (to which she presumably refers), equates to removal from the body. Earlier studies on test animals show that mercury from Thimerosal injections was 75% eliminated from the blood in six hours, and that while this drop in blood mercury occurred, the mercury level in the brain, liver, and kidney increased two- to threefold [91]. It would be very unwise to underestimate the toxicity of ethyl mercury. In 1977, multiple applications of unquantified amounts of antiseptic levels of Thimerosal to the skin of thirteen babies with neonatal umbilical complications resulted in the death of ten of the infants [92]. A recent monkey study found that the way the body handles Thimerosal (ethyl mercury) is quite different and potentially more dangerous to the developing brain than the way it deals with methyl mercury [89].

"Is it possible that mercury causes autism? No. Mercury poisoning, also known as Mad Hatter's Disease, is very different from autism. Symptoms of mercury poisoning include excessive sweating, tremors and kidney problems. Sufferers also talk and walk like they have had a stroke." But Mad Hatter's Disease is due to poisoning caused by the inhaled vapor of mercurous nitrate [93], an inorganic mercurial that is very different from the ethyl mercury in vaccines and methyl mercury in tuna. "Sweating, tremors, and kidney problems" ignores the very wide spectrum of clinical outcomes from toxic mercury exposure [94]. Moreover, the age of exposure is key to outcome. Infants exposed to mercury risk damage to neuronal connections that are forming. Adults exposed to mercury are at risk of having established neuronal connections disrupted. In fact, environmental mercury exposure has emerged in autism research as one of the most consistent risk factors [95-99].

Brown's statements add further to the confusion: *"The information known about mercury poisoning comes from unfortunate communities that have experienced it. There is a large amount of data from the Faroe Islands, near Iceland. The people there would eat whale blubber contaminated with toxic levels of methyl mercury and polychlorinated biphenyls (PCBs). Children, especially those exposed as fetuses during their mother's pregnancy, seemed to have lower scores on memory, attention, and language tests than their unexposed peers."* But now she's talking about methyl mercury, not the mercurous nitrate that causes Hatters to drool and wobble, or the ethyl mercury in vaccines.

"Another key point: mercury preservative was taken out of required vaccines SEVEN years ago. But autism rates are still going up."

Physicians were permitted to use up available stores of Thimerosal-containing vaccines from their shelves, and it remains an ingredient in some flu vaccines, which are on the list of the CDC's recommended childhood vaccinations. State legislation allows for the use of Thimerosal-containing vaccines without liability, even in those states where it has been ostensibly removed from vaccines. Pregnant women were identified as a target population for flu shots around 2002 [172]. In Minamata disease, which occurred following accidental methyl mercury poisoning, exposures that were not evidently toxic to pregnant women produced crippling disabilities in their offspring [100].

"Did the mercury in vaccines cause autism? No. Here is the scientific evidence: the Institute of Medicine [IOM] spent four years studying this issue. Their conclusion, issued in 2004: mercury preservatives in vaccines did NOT cause autism and the Institute said it was time to move on to look at other possible causes."

The IOM's unfortunate tendency to rely almost exclusively on population data has already been discussed. In fact, the IOM did not state, nor could they have stated, that mercury preservatives in vaccines did NOT cause autism. They stated that the epidemiological evidence favors rejection—nowhere near as definitive as Brown states.

IOM member and former National Institutes of Health Director Dr. Bernadine Healy caused a furor when she differed with some of her colleagues on this matter in an interview with CBS's Sharyl Attkisson on May 12, 2008. Healy decried the atmosphere of censorship that has pervaded the question of vaccines in autism, stating: "The government has said in a report by the Institute of Medicine, and by the way I'm a member of the Institute of Medicine—I love the Institute of Medicine—but a report in 2004 basically said 'do not pursue susceptibility groups—don't look for those patients—those children who may be vulnerable.' I really take issue with that conclusion. The reason why they didn't want to look for those susceptibility groups was because they were afraid that if they found them, however big or small they were, that that would scare the public away." She affirmed that, "there is a completely expressed concern—that they don't want to pursue a hypothesis because that hypothesis could be damaging to the public health community at large by scaring people. First of all, I think the public's smarter than that. The public values vaccines. But more importantly, I don't think you should ever turn your back on any scientific hypothesis because you're afraid of what it might show. Dr. Healy went on to say, "When I first heard that there was a link between autism and vaccines, I thought that was silly. Really, I tended to dismiss it just on the superficial kind of reading, just reading what was in the papers, no offense to the media—so when I first heard about it I thought 'well, that doesn't make sense to me.' The more you delve into it, if you look at the basic science, if you look at the research that's been done in animals, if you also look at some of these individual cases, and if you look at the evidence that there is no link, what I come away with is the question has not been answered."

During the CDC Scientific Review of Vaccine Safety Datalink Information (the Simpsonwood Meeting) in 2000 [101], Dr. Clements, perhaps believing that his words would never reach the ears of the public, was even more candid: "Perhaps this study [102] should not have been done at all, because the outcome of it could have, to some extent, been predicted, and we have all reached this point now where we are left hanging…." [101]. This meeting, which saw the systematic and deliberate post hoc re-analysis of data on neuro-developmental disorders in Thimerosal recipients, specifically in order to eliminate statistically significant associations, is a key juncture in the process of loss of public confidence in vaccine regulators [103].

Finally, it is important to note that a subsequent 2008 IOM autism workshop reversed much of the Institute's original position, concluding that vaccine safety was "still on the table" and recommended specific vaccine studies [104].

"A study in 2007 showed that children between seven and ten years of age who got those mercury containing vaccines (before 2001) had no significant differences in tests of attention and processing information. Although the study did not look specifically at autism, it showed that mercury preservatives did not make much of an impact on brain functions in general."

This study by Thompson, *et al*. [86] had a pitiful response rate from participants (30%) compared to the 70-80% that is usually required for the publication of a study of this sort. Moreover, how could a study that looked at neurological outcomes (but not autism) in children and showed that "mercury preservatives did not make much of an impact on brain functions in general" be terribly reassuring when any negative impact of an avoidable risk would be of concern? This very study even confirmed earlier findings of an association between Thimerosal exposure and motor and verbal tics, and lower language ability. This alone is cause for alarm [86].

Even more worrying are the results of a recent study from the State University of New York (SUNY) that boys in the United States who were vaccinated with the triple series hepatitis B vaccine during the time period when vaccines were manufactured with Thimerosal, were nine times more susceptible to developmental disability than were unvaccinated boys [105].

"Do vaccines still contain mercury? What about the flu vaccine? In 2001, the FDA required manufacturers to discontinue using mercury preservative for ALL routine childhood vaccines. Period."

The FDA has made no such requirement. Most flu vaccine doses contain Thimerosal and, based on the advice of the Advisory Committee on Immunization Practices (ACIP), [106] the CDC currently recommends these vaccines for routine inoculation of all children 6 to 215+ months of age and women pregnant during the flu season. Since 2002, the CDC has recommended this routine inoculation of pregnant women with flu vaccines although the FDA has not approved the use of any of influenza vaccine for administration to pregnant women.

Thus, it appears that the CDC's recommendation to give inactivated influenza vaccines to pregnant women—an unapproved use—constitutes the illegal promotion of an off-label use, which is a serious violation of drug law, as the recent $2.3 billion dollar settlement by Pfizer over a federal inquiry into its off-label marketing of Bextra [173] clearly demonstrates.

Moreover, it is clear that the FDA has continued to illegally approve Thimerosal-preserved vaccines because, although it is required by law (21 CFR § 601.4(a)) that the FDA obtain all the required safety studies before approving any biological drug product, the FDA has approved such drugs without requiring the makers of Thimerosal-preserved vaccines (who have, to date, admitted failing to conduct and submit in their Biological Licensing Application (BLA) all of the requisite safety studies). [At *a minimum*, the producers of Thimerosal-preserved vaccines are required by law to conduct and submit *scientifically sound* and *appropriate* toxicological safety studies proving that the Thimerosal level in their preserved vaccine product formulation is "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient …" (21 CFR § 610.15(a)).]

Therefore, the FDA has *knowingly* and *illegally* approved Thimerosal-preserved vaccine formulations since 1973 when the legal responsibility for vaccine licensing and approval was transferred to them.

Finally, since the requirements set forth in 21 CFR Parts 600 through 680 are current good manufacturing practice (CGMP) requirements, all Thimerosal-preserved vaccines are adulterated drugs by statute, 21 U.S.C. § 351(a)(2)(b), and by regulation (law), 21 CFR § 210.1(b).

"Because the flu vaccine is reformulated each year for the upcoming season, manufacturers need to move as efficiently as possible to produce large quantities of vaccine. The best way to do this is to produce vaccine in multi-dose vials, which requires a preservative. There are, however, single-dose preparations that are FREE of mercury preservatives that can be given to young children and pregnant women, if available. Let's do a reality check here: a tuna sandwich has FIVE TIMES more mercury than one dose of flu vaccine."

It is a safe bet that not too many infants eat tuna sandwiches at six months, but as previously emphasized, the mercury in vaccines and that in tuna differ, so the two are not directly comparable. Moreover, the risks associated with the different routes of exposure (ingestion for the "tunafish sandwiches" versus injection for the Thimerosal-preserved vaccines) are significantly different. In eating a complex food containing tissue-bound mercury species, the person's digestive system contains metallothionen compounds that reduce the amount of mercury that enters the body to some fraction of the mercury in that food. In contrast, all of the mercury in a vaccine enters the body.

The reason for multidose vaccines—and therefore Thimerosal—has nothing to do with the manufacturers "*need to move efficiently,*" but cost. The cost of a shot from a multi-dose vial is less than half of that from a single-shot vial [93]. Such decisions should be taken without concern for cost in order to provide children with the safest alternatives.

"As a doctor, I am much more concerned about mercury exposure in the environment—particularly in food (like that tuna fish sandwich). So if you are worried about mercury exposure, consider this: there's mercury in breast milk. A baby gets 25 times more mercury by breastfeeding for six months than in a single dose of flu vaccine. Breast milk contains between 1.4 and 1.7 micrograms of methyl mercury per liter. If you assume that a baby is breast-fed exclusively up until six months of age, that baby will consume about 360 micrograms of methyl mercury. That's twice the amount of mercury that was ever contained in vaccines and 25 times the quantity of mercury contained in the influenza vaccine."

At the risk of belaboring the point, ethyl and methyl mercury are different. Nonetheless, given the toxic load of mercury to which children are currently exposed even in the absence of vaccines, let's not be oblivious to the added risk of exposing infants to extra mercury in vaccines, potentially pushing them to a level that is dangerous and damaging. The mercury in breast milk has been exposed to the protective proteins in the mother's human toxic-protection system. Also, the 360 micrograms/6 months is about 360 micrograms/180 days or 2 micrograms/day of methyl mercury, delivered over a 24-hour period. A vaccine contains 12.5 to 25.0 micrograms of ethyl mercury, and this 6- to 12-fold increase is injected instead of ingested and is delivered within one minute. In some vaccines, it is also combined with polymeric aluminum hydroxy materials used as an immune-system activator (adjuvant), which has been shown to raise the potential toxicity of Thimerosal [107].

"What do you think of delaying vaccines or using an alternative vaccination schedule? The CDC publishes a recommended vaccine schedule for all children in the U.S.—this schedule wasn't created from thin air ... doctors, scientists and researchers work together to decide what is the best time to give shots. The goal: protect as many babies as soon as possible from deadly disease. Now, one of the popular myths about autism is that somehow kids are getting 'too many shots, too soon.' Despite the scientific evidence that shows vaccines do NOT cause autism, some parents think that if they space out their kids' vaccines in an 'alternative schedule' this is somehow safer. Adding to this notion are blogs, books, and web sites that promote alternative vaccine schedules, delaying critical shots months or years after a child can safely receive them. Here's a nasty little truth about alternative vaccination schedules: they are all fantasy. There is absolutely no research that says delaying certain shots is safer. Doctors who promote these schedules are simply guessing when to give which shots."

Many people are astounded by Brown's particularly outspoken position. Several research teams have dispelled this myth. Here is but one example of the *"absolutely no research"* that says delaying certain shots is safer: several

studies have linked asthma to DPT vaccine exposure [108]. Since the findings have been contradictory, McDonald, *et al.* from the University of Manitoba reasoned that, as with MMR and autism, this could be due to different timing of DPT vaccine in different studies. They looked at the timing of DPT immunization and its risk of childhood asthma by age seven. The complete immunization and health care records of 11,531 children from birth until age seven were analyzed. They found that the risk of asthma was reduced to one half in children whose first dose of DPT was delayed by more than two months compared with those children first vaccinated according to schedule (two months). The likelihood of asthma in children with delays in all three DPT doses was reduced still further, to just over one third of the risk of those vaccinated on schedule (at two, four, and six months). Moreover, children who received the vaccine earlier than the recommended schedule had a 60% increased risk compared with those vaccinated on schedule [108].

The findings provide strong evidence not only that DPT vaccine is causally associated with asthma, but also that the size of this risk is influenced by age of vaccination. Delaying DPT vaccination was found to be protective against asthma, a common, serious, and potentially fatal disease. It is a "nasty little truth" that according to the American Academy of Allergy, Asthma, and Immunology, asthma kills 5,000 people per year in the US, a number that may be dramatically impacted by an alternative vaccine schedule. While there are other examples [109-113], this study alone is sufficient to refute Brown's arguments.

"Also: spreading out vaccinations creates new challenges. Live vaccines must be given at least four weeks apart to mount an active immune response. Take the MMR (measles, mumps, and rubella) vaccine—your child could get one combo shot and take care of all three deadly diseases at once. If you get three separate shots, however, it would take at least three months (because each is a live vaccine). That leaves kids unprotected until the series is completed."

This issue is often dramatized in order to coerce parents into compliance. Here measles, mumps, and rubella are portrayed as "*deadly diseases."* In reality, mumps is a mild childhood illness for which death is extremely rare in recorded literature [114]. Rubella is such a trivial, harmless disease in children that vaccination is given not to protect the child, but rather to protect childbearing women from exposure by creating herd immunity. Measles is rarely fatal in developed-world children. In the US, as in other developed countries, measles mortality was falling long before vaccination was introduced. Extrapolation of the US mortality trend indicates that even in the absence of vaccination, measles mortality in the US would have fallen to vanishingly low levels by 2010 [115].

"What we know for certain is that delaying your child's shots is playing Russian Roulette. The simple truth is you are leaving your child unprotected. Who knows what disease (preventable from a simple vaccine) will crop up next? Deadly diseases like measles are only a plane flight away."

There is no such thing as a simple vaccine. And, no—Russian roulette has a one in six chance of certain death. This is an example of the kind of scare tactics that have no place in a rational discussion on the timing of a child's vaccinations.

"At the end of the day, I just want your child vaccinated. If you want to give two shots today and two next week, that's okay. Just come back. And promise me you will do it in a timely manner (that means you return in weeks, not months or years, to finish vaccination): The goal: make sure the child is protected."

For those parents who are still not convinced and still would like a spaced out vaccination schedule, this is an insistent plea. But it's confusing, since Brown just told us that, *"Live vaccines must be given at least four weeks apart to mount an active immune response."*

"One important point to remember: despite all the media attention to this subject, very few parents actually choose to delay or opt out of vaccinations."

Of course, it's fair to assume the majority are compliant because coercive mandates exclude children from public school and certain welfare benefits unless they are up-to-date on their vaccines.

"Are vaccines really necessary? Yes. As a doctor, I am greatly worried when parents decide to delay or not to vaccinate their child. That's because vaccine-preventable diseases are real. I have watched a child die from a vaccine-preventable disease while I helplessly stood by. I've cared for several babies gasping for breath with whooping cough. These diseases kill children. Respect them. Last year alone vaccines prevented 14 million infections and 33,000 deaths in the U.S. Our grandparents remember diseases like polio. And how folks lined up to get vaccinated. Yet, you've probably never even heard of anyone with polio today. The great irony of vaccine success is that parents today are unfamiliar with the diseases they prevent."

While this is a valid scientific question, whether or not vaccines are necessary is a much broader issue that will be examined and discussed at a later date. What we are actively advocating for now is a vaccine strategy that puts safety first. Parents of children with autism have presented us with focused safety concerns: the combination MMR vaccine and the presence of known neurotoxins such as Thimerosal in vaccines. Separating the M, M, and R, and removing the toxins would not lead to deaths from preventable disease. The reference that is made to polio and other vaccines is dishonest *because, provided they are Thimerosal-free and contain safe adjuvants, they usually are not considered to be causal factors in autism.*

Brown cites recent measles cases as evidence of possible resurgence of the disease, pointing the finger at parents who claim exemption for philosophical or religious beliefs. She dwells upon babies who caught measles when too young to be vaccinated. Historically, babies were never susceptible to measles, because maternal antibody (passive immunity) protected them through their first year of life. This changed following the introduction of measles vaccine. Women who are vaccinated against measles in childhood do not confer adequate passive immunity on their infants. So one unforeseen and paradoxical consequence of vaccination is increasing measles susceptibility in infants.

"So, when people argue that kids get too many shots today, I ask them if they'd rather their child get meningitis."

Emotional blackmail does not serve to lessen the parent's safety concerns. Rather, it continues the tradition of doctors blaming parents and is ethically dubious.

"And what about vaccines in the pipeline? If we've already got too many shots, would you decide to skip a future vaccine to prevent HIV? Probably not. That's because you know that vaccine might be the one that saves your child's life."

A decision to undergo vaccination against HIV would clearly depend upon the indication for, and merits of, that hypothetical vaccine.

"Didn't the government recently concede that vaccines caused autism? As you may have heard on the news, the government recently decided to compensate a child whose autism was allegedly triggered by a vaccine. Here's the background behind the headline: The Vaccine Injury Compensation Program has been holding special hearings called the Omnibus Autism Proceedings. This 'Vaccine Court' is looking at allegations that 4900 children developed autism from vaccines. The court is first looking at nine cases to form opinions about the evidence. One child, Hannah Poling, was awarded a monetary settlement. Hannah was born with a rare genetic disorder (mitochondrial disorder, which is a dysfunction in basic cell metabolism). This is the equivalent of being born with an undetected heart defect—a ticking time bomb that could go off at any time."

Hannah was not born with a *"rare genetic disorder."* Her mother had the same genetic change, without any clinical disorder. What actually happened, in the words of her father, a neurologist writing in the *New York Times*, was that, "Our daughter, Hannah, developed normally until receiving nine vaccines at once. She immediately developed a fever and encephalopathy [impaired brain functioning], deteriorating into….autism" [116].

With respect to the potential origins of Hannah's mitochondrial dysfunction (a defect in the "batteries" that provide energy to the body's cells), the authors of the original paper, in describing her condition, wrote*:* "It is unclear whether mitochondrial dysfunction results from a primary genetic abnormality, atypical development of essential metabolic pathways, or secondary inhibition of oxidative phosphorylation [e.g., poisoning the cell's ability to use oxygen to produce energy] by other factors. If such dysfunction is present at the time of infections and immunizations in young children, the added oxidative stresses from immune activation on cellular energy metabolism are likely to be espe-

cially critical for the central nervous system, which is highly dependent on mitochondrial function" [117]. In other words, vaccination might push a vulnerable system over the edge, causing brain damage.

Moreover, though Hannah Poling had been selected as a "Thimerosal causes autism" test case in the Omnibus Autism Proceedings because she had been found to be mercury- poisoned by the perservative-level doses of Thimerosal, medical professionals in the Department of Health and Human Services, after reviewing Hannah Poling's medical records but not the reports of the experts who were scheduled to testify on Hannah's behalf, conceded her case before there was any hearing in the "Vaccine Court." Thus, the account provided is not only inaccurate but it is also misleading.

"For rare kids like Hannah, any stress could have caused her to develop autism. In fact, having a vaccine-preventable disease like the flu or chickenpox could have far worse health consequences—a disease like that could have killed her. Although she was not diagnosed prior to being vaccinated, experts recommend that even children with known mitochondrial disorders still be vaccinated."

Hannah was not diagnosed prior to vaccination because she had no disease to diagnose. She was perfectly well before vaccination. The "expert" opinion cited is not referenced.

Brown is emphatic: "*Experts on mitochondrial disorders do NOT think this disease is the 'smoking gun' that triggers autism. That's because many folks have similar dysfunctional cells but never become autistic*."

This is correct: experts do not think that mitochondrial disorders trigger autism. As Hannah's case illustrates, it was the vaccines that triggered her autism—her possibly pre-existing mitochondrial dysfunction[a] *might* have been an underlying susceptibility factor.

It is very confusing for parents to read that children like Hannah are rare, followed by the contention that many people have similar dysfunctional cells. Which is it? Estimates in June 2008 were that 20% of autistic children have mitochondrial disorder [118] and up to 50% of the approximately 4800 cases currently filed in the US federal vaccine court might show markers of mild mitochondrial dysfunction. As many as 1 in 50 to 1 in 200 children might carry the DNA mutation that predisposes them to vaccine-induced mitochondrial disorder [119-121]. The case of Hannah Poling [117], and that presented by Filipek, *et al.* demonstrate subtle abnormal biomarkers of mitochondrial function, and are consistent with the fact that children with autism have an increased incidence of mitochondrial disorders [122].

"And there is no simple test for mitochondrial disorders. Instead, you must do a difficult and painful muscle biopsy and a spinal tap. As a result, testing all kids for mitochondrial disorders is not necessary, ethical or practical. And even if your child is diagnosed with a mitochondrial disorder, the recommendation is still to vaccinate."

Brown contends that a mitochondrial disorder was present in Hannah and was responsible for her autism. The experts caring for Hannah and the medical experts at The Department of Health and Human Services agreed that multiple vaccinations, possibly in combination with her underlying (clinically silent) mitochondrial dysfunction, led to her being diagnosed with autism and epilepsy. Up to half of the 4.8 thousand children in vaccine court might have mild mitochondrial dysfunction, possibly reflecting a shared susceptibility. And yet Brown's position on vaccinating children like Hannah remains steadfast. How many cases like Hannah's would it take for vaccine regulators to exhibit a modicum of concern?

And what *do* the "experts" say about vaccination of children with mitochondrial dysfunction? Dr. Douglas C. Wallace is one of the world's leading mitochondria researchers. He is Professor of Pediatrics (Human Genetics Division and Metabolism), Professor of Biological Chemistry, Director of the Center for Molecular and Mitochondrial Medicine and Genetics at the University of California-Irvine, and a member of the United Mitochondrial Disorders Foundation's (UMDF) Scientific and Medical Advisory Board. In commenting on the report of Poling, *et al*. [117] he said, "This new study suggests that mitochondrial dysfunction is a major underlying risk factor for human disease" [123]. In April, he told the Vaccine Safety Working Group of HHS's National Vaccine Advisory Committee that over-vaccination of people with mitochondrial disorders was a deep concern, especially in light of Hannah Poling, who got nine vaccines in one well-baby visit [123].

"We have always advocated spreading the immunizations out as much as possible because every time you vaccinate, you are creating a challenge for the system," Wallace testified. "And if a child has an impaired system, that could in fact trigger further clinical problems." Clearly, his position is not consistent with that of the experts cited, but not referenced, by Brown.

"Does the MMR vaccine cause autism? One small study of only eight patients in 1998 led a British research group to conclude that the combination MMR vaccine might cause autism. But in March 2004, after questions were raised about the study, ten of the 13 researchers of the study withdrew their claim of having found a possible connection between MMR and autism. They said, "In this paper, NO CAUSAL LINK was established between MMR vaccine and autism as the data were insufficient…now is the appropriate time that we should together formally retract the interpretation of the data suggesting a link."

It is a common oversight to ignore other papers that have described or examined a link between MMR vaccine and autism [124-131]. Additionally, most people might not know that some of the authors were persuaded by *The Lancet's* editor, Dr. Richard Horton, to issue a partial retraction of an interpretation of a possible link between MMR and autism in the children described—six years after the original paper was published. But you cannot retract a possibility, and therefore the possibility remains. The partial retraction was urged on the basis that one of the authors of this document (AJW), and the lead author on the *Lancet* paper, had agreed to act on behalf of children involved in the MMR litigation. Horton has claimed that this fact had not been made known to him prior to publication and that Wakefield was in breach of the *Lancet's* disclosure requirements. It has since emerged as a matter of record that not only did Wakefield follow the *Lancet's* disclosure requirements to the letter, but also that Horton was informed of his involvement in the litigation one full year before the *Lancet* paper was published [132].

"Numerous major studies (at least 17 so far) since 1998 also soundly refute this alleged link. The most prominent: the Institute of Medicine's 2004 report clearly dispelled any link between MMR and autism."

Most critics fail to reference the authoritative Cochrane review of these studies—exclusively non-clinical—which dismissed most of the "*major studies*" upon which the IOM relied as being of insufficient quality to merit consideration. This includes the work of Eric Fombonne [133], of which the review said, "the number and possible impact of biases in this study was so high that interpretation of the results was difficult" [134]. Further, in an extraordinary paper, "Tale of Two Cities" [135], Dr. Fouad Yazbak uncovered how Dr. Eric Fombonne mixed data from two Canadian cities, Montreal and Quebec City, to create the misleading impression that autism had gone up when MMR uptake was falling [136]. Dr. Yazbak's investigation showed that when autism and MMR uptake rates in the same city (Montreal) were compared, both went up [135]..

More importantly, however, data that have been represented to the public as showing no association between MMR and autism in fact show just the opposite. A case in point is the CDC's own study looking at age-at-first-MMR vaccination and autism risk [137]. The study found a statistically significant association between younger age at MMR vaccination and an increased risk of autism. This risk was greatest in the most recently vaccinated children. Why? The age at first MMR vaccination has gone down over time [138, 139]. Edwardes and Baltzan [139] confirmed that the age at MMR immunization was becoming younger over time and that the rate of early MMR immunization is correlated with the incidence of autism. This would explain why the most recently vaccinated children in the CDC study were at greater risk— they were very likely vaccinated at a younger age.

Alarmingly, having tested a hypothesis and found a significant association between autism risk and age of first MMR exposure, the authors tried

[a] In the Amended Respondent's Report, issued after review of the experts' reports and additional medical records and filed 02/21/2008 by Secretary of Health and Human Services, (Watts, Lisa) [document 27 in the case history for *1:02-vv-01466-UNJ POLING, et al. v. HHS*], the finding of "mitochondrial disorder" (in the original Respondent's Report, filed 11/09/2007 [document 17]) was amended to "mitochondrial dysfunction" and conceded both Hannah's "autism" and "seizure disorder" were causally linked to the 9 vaccines Hannah received in one office visit when she was nominally 19 months of age.

to explain away this effect to an "artifact of immunization requirements for preschool special education attendance in case [autistic] children." Such an interpretation could only be valid if the immunization mandate for normal prechool children were different from that of special education children, but it is not. Moreover, the special education group, with a likely excess of contra-indications to MMR vaccination such as seizures, should have a lower uptake percentage for MMR vaccination. In addition, if there were no true association, lower exposure in the special education group would be expected in light of higher levels of parental concern and consequent rates of abstention in this group—a possibility that could have been easily checked by comparing the proportions of exemption filings upheld by law in all state schools. A similar association between younger age of MMR vaccination and increased risk for autism has been shown in the data from several other studies touted as being proof that MMR and autism are not linked [126, 139, 140]. Is it any wonder that parents and professionals are confused?

The association between autism risk and age of MMR exposure would also provide an explanation for why the incidence of autism has continued to rise, since the risk from MMR would have changed over time as the recommended age of MMR vaccination has been lowered, potentially putting more children at risk.

"Perhaps the most compelling argument that the MMR vaccine does NOT cause autism is Japan—in 1993, that country stopped using the combination MMR vaccine. Instead, Japanese children were given three separate shots for these diseases. Despite this change, autism rates in Japan continue to rise."

In fact, the Japanese data [23] provide some of the strongest evidence yet of a link between exposure to measles-containing vaccines and autism. Unlike any epidemic pattern elsewhere in the world, the Japanese data show an initial increase in autism incidence in the first recipients of MMR, followed by a declining incidence when MMR was abandoned due to complications. MMR was never reintroduced there. Instead, a new policy was eventually formulated, and children received measles and rubella on the same day, followed by mumps vaccine around four weeks later. This, in effect, gives overlapping exposures tantamount to the combined MMR vaccine, since the live viruses remain and reproduce within the child during a short period. This policy was never tested for safety, and autism incidence went on to triple from $55/10^5$ for those born in 1991 to $161/10^5$ in children born only three years later.

"The hysteria surrounding the MMR vaccine and the false 1998 report did have one serious consequence in England: a sharp rise in measles, mumps, and rubella after parents stopped giving their kids the vaccine. In 2004, only 40% of children in the U.K. were vaccinated against MMR. And look at the rise in cases of mumps: 1995: 1936 cases; 2003: 4265 cases; 2004: 15,503 cases."

There was nothing "*false*" about the *Lancet* 1998 paper, which has been willfully misrepresented. The paper discussed a possibility, raised by parents, that MMR causes regressive autism, and the authors encouraged further research on this subject. Explicitly the paper stated, "We did not prove an association between measles, mumps, rubella vaccine and the syndrome described" [141]. An "association" was not proven, let alone a "causal" association. The paper did not shirk from reporting the parental stories of regression following MMR vaccination in some children, nor should it have.

What *is* false is the claim that "*in 2004 only 40% of children in the U.K. were vaccinated with MMR.*" Official figures show that uptake of primary (initial) MMR vaccination in the UK never fell below 80% from 1996 to 2007 [142].

Brown also fails to mention the fact of the high primary and secondary failure rate for the mumps component as indicated by recent outbreaks of mumps in highly vaccinated populations [143-146].

"Are we giving too many vaccines today, too soon? Look at it this way: your child is exposed to thousands of germs on a daily basis (even if he is not in daycare). Exposing your child to five or eight different germs in the form of vaccines is a spit in the bucket. And young kids have a better immune response to vaccines than older children and adults."

In referring to "*germs"* it is not clear if she is talking about microbes (i.e., bacteria and viruses) or pathogens (i.e., bacteria and viruses that cause disease). The difference is crucial. While children are exposed to many microbes every day, many of which—like normal gut bacteria—are vital for good health, there is absolutely no evidence whatsoever that children are exposed to thousands of pathogens every day. Since she refers to germs in relation to vaccines against pathogens, presumably this passage is equating germs with pathogens. Thus, she appears to be claiming that children are exposed to thousands of disease-causing organisms a day, a claim that is not only incorrect and wholly misleading but also ridiculous.

"Before a vaccine is approved for use by the government, its safety is extensively studied. These studies look at how kids respond to the vaccine. And so-called 'combo' vaccines that incorporate several shots at once also consider the combined effect."

Opinions that bear upon this view of safety testing are available from several official sources. Since we are talking autism, let's examine her claim to the "*extensive*" studies; first, in the setting of preclinical neurotoxicity testing prior to experimentation in children. The World Health Organization (WHO) provides recommendations to vaccine manufacturers for the preclinical safety and efficacy testing of individual measles, mumps, and rubella vaccines for human use [147]. They require that tests to reveal the ability of the virus to cause disease within the brain or nervous system be conducted as follows: At least ten primates (after a blood test showing they are negative for the virus) should be employed in each test. The material [vaccine-strain virus] being tested should be given by injection to the brain, and the total amount of virus given to each animal should not be less than the amount contained in the recommended single human dose of the vaccine.

To be clear, this means that the virus alone—not the vaccine with all its additives—is injected directly into the brain. WHO requires that injected animals should be observed for 17-21 days for symptoms of paralysis and other evidence of neurological involvement. Animals that die within 48 hours of injection can be replaced, and the test is considered invalid and should be repeated if more than 20% of the animals die. This is startling, and the logic is unclear: if the virus is bad enough to either kill an animal within 48 hours or kill 20% of the animals during the course of the testing, then are we to conclude it is the fault of the animal(s) and not of the vaccine virus?

At the end of the observation period, each animal is bled and its blood tested for virus antibody (indicating efficacy), followed by an autopsy to include histopathologic (microscopic) examinations of the brain for evidence of central nervous system (CNS) involvement. The virus is considered "safe" if there is no clinical or microscopic evidence of involvement of the CNS attributable to the injected virus. But this is impossible to assess since no control animals were required in the experiment, i.e., animals who received a saline injection instead of virus.

It is evident to anyone that, far from being *"extensive,"* the WHO requirements for this aspect of preclinical vaccine-safety testing are wholly inadequate and largely irrelevant; of particular concern is the fact that there is no requirement for the safety-testing of "*combo vaccines*" (e.g., MMR), or the infant vaccine regimen. By studying individual vaccine components only, there is the potential to miss cumulative and synergistic toxicities, as well as possible immunologic interference that might alter the safety of the vaccine regimen. Thimerosal has well-established neurotoxic [148-150] and immunotoxic [151-153] potential. Theoretically, the effects of Thimerosal and of aluminum-containing adjuvants individually, additively, or synergistically, could increase the risk of an adverse response to a live viral vaccine. By analogy, no sane regulatory agency would ever license a "combo" of three anti-hypertension (blood pressure) drugs without rigorous safety-testing of the risks of the combined product compared with those of the individual component drugs.

Clinical studies are no more reassuring. The IOM, previously cited by Brown, had the following to say about vaccine safety:

> "In the course of its review, the committee encountered many gaps and limitations in knowledge bearing directly and indirectly on the safety of vaccines. These include inadequate understanding of the biologic mechanisms underlying adverse events following natural infection or immunization, insufficient or inconsistent information from case reports and case series, inadequate size or length of follow-up of many population-based epidemiologic studies, and limited capacity of existing surveillance systems of vaccine injury to provide persuasive evidence of causation. The

committee found few experimental studies published in relation to the number of epidemiological studies published. Clearly, if research capacity and accomplishment in these areas are not improved, future reviews of vaccine safety will be similarly handicapped" [154].

The deficiencies in vaccine safety studies were later reinforced by the systematic analysis of Dr. Thomas Jefferson and colleagues from the Cochrane Collaboration, an internationally respected body that provides independent scientific oversight. They wrote, "The design and reporting of safety outcomes in MMR vaccine studies, both pre and postmarketing is largely inadequate" [134]. In an interview with Richard Halvorsen for his book *The Truth about Vaccines*, [155] one of the lead authors of the Cochrane review left no doubt as to his true feelings when he said, "The safety studies of MMR vaccine are crap. They're the best crap we have but they're still crap" [156].

And what of the policy makers? The CDC, in its draft plan for immunization safety research, makes the alarming admission that, "Usually simultaneous vaccination is incompletely studied at time of licensure" [157]. Blaxill [158] captures the "incompletely studied" mindset of the CDC's National Immunization Program (NIP) when he cites Dr. Robert Chen "the man most responsible for setting the tone and direction of NIP safety practices for over a decade." Writing in 1999, Chen stated, "[W]e have been relatively slow in appreciating the importance the public now places on vaccine safety. In fact, much of our resource allocations still unfortunately reflect safety last rather than safety first….Furthermore…we have not been as interested in preventing vaccine-induced illnesses as we are with vaccine-preventable diseases" [159].

But there is reason for even greater concern. Brown claims that: "*Even if your child got 11 shots at the same time, he would need to use only about 0.1 % of his immune system to respond to the vaccines*."

Her claim is based upon a wholly theoretical argument put forward by Dr. Paul Offit in 2002, in a published paper in which conflicts of interest are not declared [160]. It starts with an estimation of the capacity of the immune system to respond to a huge diversity of antigens (fragments of infectious agents that are recognized as foreign), based upon the number of possible permutations in the human genes that encode for antibody production. It is unlikely that any immune system in the history of mankind has ever been required to respond in this way. Offit goes on to pursue an equally speculative argument when he claims, "A more practical way to determine the diversity of the immune response would be to estimate the number of vaccines to which a child could respond at one time." In doing so, he equates a tenth-grade multiplication exercise with safety. Making a naïve argument, evident even to a non-immunologist, he contends that because we each have a lot of cells capable of producing antibodies, then there should be enough to go around enough, in fact, for a child to respond to 10,000 vaccine antigens at once or so he claims. Let's use the analogy that because you have five million bricks you can build a hospital; the elaboration of an immune response, like the building of a hospital, requires the orchestration of a number of highly complex events. In Offit's scenario all the building materials and construction workers turn up at the site on the same day; chaos is inevitable. Different infectious agents (or their antigens) effectively compete for the attention of immune cells with the result that they interfere with the response to one another, confusing the immune system. This happens with unpredictable consequences for protective immunity and unknown implications for safety.

In 1977 the FDA wrote that, "Experience has shown that combining monovalent vaccines may result in a new combination which is less safe or effective than desirable" [161]. This was observed, for example, with measles and mumps vaccines in the MMR [162, 163]. For MMR combined with chickenpox vaccine, interference altered the immune response still further, such that ten times the amount of chickenpox virus was required to produce the same response with the combined vaccine, compared with the single chickenpox vaccine given alone. In 2008, the Advisory Committee on Immunization Practices (ACIP) recommended withdrawal of ProQuad® (Merck's MMR + varicella vaccine) because it doubled the risk of seizures compared with the vaccines given separately [164]. Imagine the utter chaos of 10,000 competing vaccines.

"*The goal is to protect your child as quickly as possible from diseases that are very dangerous to young children. And even though the number of shots has gone up, the actual load on the immune system has gone down. That's because today's vaccines are 'smarter' and better engineered than the shots from a few decades ago."*

The goal should be to protect your child as safely and effectively as possible—not as quickly as possible—from serious, preventable disease. We have no way of measuring the load on the immune system since it is an infinitely complex equation given the diversity of the genetic and epigenetic determinants of the immune response.

"Case in point: whooping cough. Before 1991, the whooping cough vaccine had 3000 different germ particles (antigens). Today's whooping cough shot has just three to five particles—just as effective, but much better designed to be easy on your immune system. Before 1996, the polio vaccine was 'live'—this carried a small risk of actually getting polio. Today's polio vaccine is dead (inactivated) and carries NO chance of transmitting the disease."

Once again, the issues that are raised, whether or not they are correct, have no bearing on the specific concerns that parents have in relation to vaccines and autism.

"So, here's the irony: YOUR parents took much greater risk when getting vaccinated back in the 50's, 60's, and 70's. Today, even though we have many more vaccines, the risk is much lower. Our children are really getting smarter, safer vaccines today and better protection than we ever got as kids. BOTTOM LINE: Vaccines do not weaken the immune system, they boost it."

A few words of caution about this line of reasoning:

- While natural "wild" measles and mumps produce life- long immunity, the vaccine strains induce weaker immune responses to these viruses, leading to susceptibility to more severe disease later in life, and the risk of dependence on repeated vaccination. At the very least, these outcomes are a public health nightmare, but, they are a windfall for the manufacturers of vaccines and the other branches of the health care establishment.
- While maternal immunity following natural measles was in the past sufficient to protect her infant for up to one year of age, passive immunity from vaccinated mothers is *weaker,* leaving the infant susceptible from early on [165]. In fact, 21st century measles outbreaks might be as likely due to this weaker passive immunity as to parents who opt out of vaccination for their children.
- Combination vaccines might result in a *weaker* immune response to the component antigens through the process called "interference" [166, 167].
- Injudicious use of measles vaccines [168] can cause long-lasting immune abnormalities and *weaker* immune responses that might be related to increased morbidity and mortality, as seen in developing countries.
- Thimerosal and aluminum push the immune response toward an allergic immune profile and increased antibody production (autoimmunity). This *weakens* the response of other parts of the immune system (e.g., cellular immunity) that are necessary for protection against viruses.
- Measles vaccines can cause immune suppression, *weakening* the immune response [169, 170].

"Are there other toxins in vaccines that could cause autism? Are there additives in the vaccines? Yes. And you should know about them. Vaccines contain the active ingredients that provide immunity. However, there are inactive ingredients that improve potency and prevent contamination. Here is a list of additives and why they are there.

1. *Preservatives—prevent vaccine contamination with germs (bacteria, fungus): 2-phenoxyethanol, phenol.*
2. *Adjuvants—improve potency/immune response: aluminum salts.*
3. *Additives—prevent vaccine deterioration and sticking to the side of the vial: gelatin, albumin, sucrose, lactose, MSG, glycine.*
4. *Residuals—remains of vaccine production process: formaldehyde, antibiotics (neomycin), egg protein, yeast protein.*

"Now, after reading the above list, you might be freaking out—aluminum salts? MSG? Formaldehyde? We should point out that only TRACE amounts of most of these additives are in vaccines. None have been proven harmful in animals or humans in these amounts."

This list of vaccine additives contains some which, far from being "*inactive,*" have potent toxic and immunologic activities. The view of what constitutes a "*TRACE amount*" is dealt with in the next section.

"Reality check: should vaccines be 'greener'? If vaccines contain in-

gredients like aluminum or formaldehyde, wouldn't it be better if vaccine makers got rid of these additives? We agree that this sounds reasonable—but it doesn't mean that current vaccines are UNSAFE. Here's the key point: additives like aluminum in vaccines are in EXTREMELY SMALL amounts (often, just a trace). We are all exposed to significantly higher levels of environmental toxins in our everyday activities. Let's look at aluminum. Babies ingest 50 micrograms of aluminum per liter of breast milk ... and 500 micrograms of aluminum per liter of formula. By contrast, the amount of aluminum in a vaccine is much smaller. Do you wear antiperspirant? That's got aluminum in it too. And aluminum is found in most food, soil, and water. So, to avoid aluminum exposure, you'd have to stop wearing antiperspirant—and basically leave the planet."

First of all, let's state the obvious: antiperspirant, soil…these items are not injected into our bodies, and certainly not into newborn babies. And let us examine the claim to the "*EXTREMELY SMALL amounts"* of aluminum in vaccines. Dr. David Ayoub provides some perspective on the current state of knowledge on what amount of aluminum is actually safe. He writes: "In spite of known toxicity of aluminum for over 100 years, no human or animal safety studies have been performed that attempted to categorize the range and potential adverse reactions or defining exposure limits from immunizations during infancy and early childhood" [171] (manuscript in preparation).

Aluminum-containing vaccines include Hepatitis A and B, DTaP, HiB, pneumococcal, and several combination vaccines. The *"trace amount"* of aluminum in the vaccines is included precisely because it is highly biologically active, boosting the antibody response to the vaccine. Indeed, it is likely that the vaccine formulations that contain such aluminum adjuvants would be ineffective in the absence of the aluminum. The FDA's per-shot aluminum limits for aluminum adjuvants are flexible: 1) 850 micrograms, "if determined by assay"; 2) 1,140 micrograms, "if determined by calculation on the basis of the amount of aluminum compound added"; or 3) 1,250 micrograms "determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research." Moreover, these limits: take no account of cumulative or simultaneous vaccine exposures, are unadjusted for body weight in contrast with most permissible toxic exposure levels, and are based on efficacy and not on safety considerations. Given the lack of studies, the safety requirement minimum for adjuvants, as set forth in 21 CFR § 610.15(a), with underlining added for emphasis: "An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product," has apparently been ignored.

"And aluminum poisoning does not cause symptoms of autism, either."

Ayoub points out that aluminum poisoning might well cause a number of features seen in autistic children, including cognitive dysfunction, speech delay, impaired socialization and eye contact, gait disturbances, and seizures [171].

Dr. Brown addresses a few other points, including the source of vaccine education information and her own belief that children with autism don't regress and lose developmental milestones. These topics, and others, will be explored in depth in a subsequent publication.

Bottom line: The US childhood vaccine schedule is a black hole, a mystery potentially fraught with unquantifiable problems. The difficulty in initiating a pragmatic response to this real public health problem (where the alternative may be a catastrophic loss of public confidence) derives from three principal sources: extraordinary biological complexity of living systems and disease, the lack of understanding of the details of all of the components of the human immune system and their interactions, and a simplistic mindset wherein belief in the proclaimed merits of mass vaccination trumps the need for rational debate.

As "informed consent" to parents who are considering the pros and cons of vaccinating a child, Brown's document—one endorsed by the Immunization Action Coalition—is woefully inadequate. It is little wonder that many parents are skeptical of the advice they receive with respect to vaccine safety; and, frankly, they deserve better.

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