Respondent's Exhibit E

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I have been asked to report my opinions of the analysis provided by Dr. Jean-Ronel Corbier concerning the nature and cause of William Yates Hazelhurst's ("Yates") developmental problems. The following represents a summary of my opinions. I have formulated these opinions upon the basis of review of Exhibits 1 – 35 provided to me as well as a review of 7 CDs labeled "Home Videos." I have organized my opinions in a sequence intended to match the organization of Dr. Corbier's report (Petitioners' Exhibit 26). The headings in quotations represent the labels that Dr. Corbier has applied to his sections. I will not comment on his statement of qualifications.

1. "Introduction": I agree with the statement that autism has attracted considerable attention and with the characterization of the "core" abnormalities of autism. I would note that interest has arisen concerning not only autism but also with the heterogeneous group of disorders termed "pervasive developmental disorders." I agree with the statement that there has been a significant rise in the "numbers of individuals who have received the diagnosis of autism in recent years," but would, in addition, state that the rise in diagnoses does not necessarily imply a rise in incidence. I state this qualification because I share the belief of many experts that the rise in the rate of diagnosis represents increased diagnostic precision, and that much or all of the rise in diagnoses of autism is mirrored by a comparable fall in the rate of diagnosis of mental retardation. Therefore, I strongly disagree with the sentence ending with "environmental triggers may have played a role in the dramatic increase in incidence of autism." There is no credible information upon which the supposition of "dramatic increase in incidence" can be based.

   The next paragraph consists chiefly of hypothetical statements. There is, however, the statement that: "Given the discovery that immune mechanisms are implicated in autism…," which is followed by another hypothetical statement. This initial portion of Dr. Corbier's syllogism is by no means "given" because it remains unproven that immune mechanisms are of importance in the pathogenesis of autism. Dr. Corbier seems to imply that inflammatory mechanisms play a pathogenic role in autism.

   To date, conventional peer-reviewed medical literature (hereinafter CPRL) only provides information concerning the possibility that immune mechanisms may play a pathogenic role in autism. The small quantity of information that has been published in the CPRL concerning the possibility that immune mechanisms play a role in autism remains controversial with regard to study methods, interpretation of results, and accuracy of data. Moreover, a significant portion of this information has become discredited.

The next paragraph of this section correctly states that Yates may be characterized as having experienced regressive autism, but the same sentence includes the unjustified conclusion that this is a condition "where environmental triggers including vaccines play an important role." There is no justification in the CPRL for such a statement. In fact, the CPRL contains strong evidence that there is no epidemiological link between vaccination and the onset of autism. Furthermore, I do not agree that a single case (Yates' case) "illustrates important factors that should be considered when discussing the etiology of autism." Conclusions drawn from selected cases without a firm foundation in standard epidemiological method are an example of the fundamental flaw in the argument that environmental factors play a role in the pathogenesis of autism.

2. "Summary of Yates Medical History": This section consists largely of statements of fact, some of which may or may not be complete. Family histories (information concerning diseases in the family of an individual with an illness), for example, are often incomplete and sometimes contain incorrect or imprecise labels for diseases experienced within a kindred. It is not clear what "held head alone" means. It should be stated that the medical record indicates that language development was delayed prior to 12 months (more than 90% of children say "mama" and "dada" before 9 months rather than at 10 months). Five additional words by 12 months would, on the other hand, represent an unusual acceleration of the acquisition of additional words after the initial "mama"/"dada."

   The available medical records do not support the statement that "regression had started at 12 months." The medical record does make note of features consistent with autism at 25 months, and does reflect that symptoms were evident around 18 months. The developmental characterization and "neurological profile" provided by Dr. Corbier apparently rely on recollections of the family that are not recorded in the medical record. These recollections should not be termed "neurological profile" since the family does not contain a neurologist. The observations are typical for autistic regression. Recollections of parents are not always accurate and are not always assigned to the appropriate time in the sequence of developmental change; on the other hand, sometimes they are.

   Dr. Corbier was impressed with "gastrointestinal and immunological disturbances." The medical records reflect some gastrointestinal problems that are not unusual in children and are of unclear significance. The record during the first year of life chiefly records normal stooling without reference to any significant gastrointestinal problems. It does not contain any evidence of "immunological disturbances." Investigation for systemic candidacies in 5/2002 was negative (no candidal antibodies detected). Immunoglobulins in August of 2002 were normal, as were complement studies, lymphocyte enumeration, and response to tetanus immunization. These findings are not mentioned in Dr. Corbier's otherwise detailed enumeration of Yates' difficulties. Lactate, ammonia, and plasma amino acids were normal in 10/02; a fragile x preparation was negative; chromosomes were normal.

   The EEG of 9/30/03 performed by Dr. Corbier demonstrated changes that are quite common in children with autism, usually during sleep rather than in the waking record—though the patient's state is not noted in this cryptic EEG characterization, nor is it noted in the official report of his EEG. Characterizing the discharge as "encephalopathic dysfunction" in his report would likely be challenged by other readers.

   "Elevation of coproporphyrins" is also cited, presumably in relationship to as yet quite unproven observations about the possibility that such a finding is representative of toxicity from environmental and other insults. It should be noted that values for these tests are not as well established in young

children as they are in the older individuals in whom they are usually ascertained. Notation of Yates' various infections does not represent an unusual profile for the otherwise normal child. "Reactive lymphadenopathy and viral URI," also highlighted, is a very common finding in otherwise normal small children. The adenopathy, in fact, is representative of the presence of normal immune response to infection.

With regard to "gastrointestinal profile," Dr. Corbier cites the finding on colonoscopy in April 2003 of nodular lymphoid hyperplasia in the sigmoid colon and rectum. It should be noted that such a finding is of unproven significance in relation to the risk for or development of autism.

My review of the medical record: Numerous observations not reflected in the medical record are appended to Dr. Corbier's recital of the sequence of immunization, and my review of the record indicates a sequence of events that is different from that provided by Dr. Corbier. There is nothing in the medical record to indicate any significant problems brought to the attention of Yates' physician prior to the 24 month visit. During preceding visits, problems are mentioned that are not different from those typically encountered in well-child visits. I can state this within a reasonable degree of medical certainty based upon 26 years of experience seeing children in pediatrics clinics, including primary care clinics in hospital and private practice settings. Problems arising from discussions with parents during these visits indicate a quite normal frequency of otitis media and some episodes of thrush that seem to be associated with times when antibiotics are given for otitis. There are several episodes of croup, not at all unusual for toddlers.

At the 18 month visit, boxes are ticked during the various office visits to indicate no parental concerns about development, behavior, psychological problems, or issues with the neurological system. As this is a parental questionnaire, presumably it was completed by the parent(s). Mention is made of lungs or breathing problems "sometimes." The parents mentioned stomach or intestine problems "sometimes." Specific mention is made of the fact that Yates' vocabulary consists of 4-10 words with emergent sound sequences suggestive of the beginnings of sentence formation. This combination of findings is normal. It is mentioned that Yates greets people with "Hi" and that he was able to imitate "hugging and loving of dolls," also quite normal for age. This history is not at all consistent with regressive autism starting at 12 months of life.

At 19 months, mention is made of "typical toddler behavior," also entirely inconsistent with regressive autism beginning at 12 months of age. At 25 months, it is indicated that the family has no concerns about gastrointestinal or neurological system issues. Mention is made of 4-10 words, which might suggest slowing of normal language development. Mention is made of the fact that Yates doesn't respond reliably to his name being called and that he doesn't always respond to sounds. He is said, however, to hug a doll. At 25 months, evaluation by Dr. Ronald Kirkland indicates that Yates' family told him that they became concerned about speech and hearing at 18 months and that at that time he was manifesting "somewhat aberrant behaviors." If this is accurate, it appears that the family has dated the onset of abnormalities to 18 months rather than 12 months.

A hearing evaluation at 26 months indicated "articulation delay" and findings on audiological evaluation suggested that otitis interna may have played a role in his diminished responsiveness to sounds. A developmental evaluation at 26 months rendered the diagnosis of autism. At 27 months, two events with paroxysmal onset occurred within approximately one hour that may have been seizures – events that, if either seizures or behavioral events, are consistent with autism. CT and EEG evaluations were normal. At 27 months, Yates had delayed cognitive and adaptive development with

noted absence of language. This represented regression in those skills. Consideration of the clinical course as reflected in the records of physician meetings with Yates and his family including parental questionnaires indicate onset of autism between 18 and 24 months.

As of 3 years of age, a series of laboratory evaluations were obtained at the Great Plains Laboratory in Lenexa, Kansas. These evaluations show elevations that are possibly consistent with fatty acid oxidation or other metabolic conditions that are genetically inherited, although the results are not consistent from sample to sample and workup to exclude these various conditions is incomplete in the records available to me. Most of the abnormalities are not necessarily indicative of metabolic disease, however, and might represent changes produced by diet. The same is true of results concerning toxic substances such as heavy metals in blood and hair. The important point to note concerning these results is that there is no known relationship between these various results and "vulnerability" to vaccination in the CPRL.

3. "Discussion": Seven bulleted statements of "Pertinent Factors" are listed at the outset of this section. The first is true. The second is not true within a reasonable degree of medical certainty. The third is not a matter of proven medical fact. The fourth is not a useful statement since a very large number of children who develop autism do not have a family history of autism, and this lack of family history is very common in many forms of autism that are known to develop on a genetic basis, characteristically so in Rett syndrome which is another form of regressive autism. The fifth is not reflected in the medical record, and even in parental recall, there is no convincing evidence of "immunological symptoms."

   The sixth bullet is in a compound state that must be disassembled to make appropriate comments. First, the medical records do not support Dr. Corbier's premise that Yates had immunological problems. Second, it is unclear whether Yates experienced seizures. Although children with autism often have abnormal EEG findings, seizures are not common. In this case, the medical record does not provide evidence for seizure events of paroxysmal nature, such as staring spells, and unresponsiveness may or may not have been seizures. I see no evidence of a relationship between vaccination and the development of autism in this case. I see no reason whatsoever to endorse the hypothesis that the various problems alleged are in any way causally linked, and would state the contrary with a reasonable degree of medical certainty. The seventh bullet alleges a "subclass of children with autism" for which there is no established identity in the CPRL. It is an unsubstantiated hypothesis, one that most of the available investigations in the CPRL do not support.

4. "Conventional View of Autism": Whatever is meant by "conventional," the information conveyed in this section is not an accurate characterization of the views held by most of the medical and scientific community that are most intensely involved in trying to understand this disorder.

   The third paragraph suggests a rejection of consideration of the possibility that autism may be increasing in prevalence. Most authorities actually keep an open mind about such possibilities but require as yet unavailable corroborative evidence before accepting such a view. It is true that many authorities believe that the increase in prevalence of diagnosis is the result of the far more accurate and careful labeling that children receive for developmental syndromes than used to be the case. There is abundant evidence that common disorders such as autism were mislabeled as static encephalopathy or mental retardation, even within our own practices. The same is true of many syndromes that we now accurately label and did not 20 or 30 years ago, such as Williams syndrome, Rett syndrome, and other syndromes with autistic features.

It is true that most established authorities reject studies implicating vaccines in autism for the very good reason that they are demonstrably flawed in design and research methods as well as interpretation. The statement that treatment strategies based on such research are unproven is because such treatments have not been demonstrated in a reproducible way to influence the course of development of an individual with autism. The same could be said about treatments that arise in the conventional medical community. The problems of communication and behavior that set an individual with autism apart from others represent a combination of poorly understood problems, many of which show improvement without specific treatments.

In fact, a number of "conventional" treatments appear to achieve improvements although additional study is necessary to validate most interventions. The appropriate degree of scrutiny to establish efficacy is independent of the theories upon which a treatment is based. It is demonstrably true that the last sentence of this paragraph is accurate and that diminished rates of vaccination may result in definite increases in the prevalence of diagnoses of severe neurological diseases in children. That fact alone would not justify the use of vaccines if they could be shown to pose a public health threat, but with the exception of very rare and unfortunate side effects of vaccines, little risk has been documented.

5. "Parental hypothesis": This section contains a bewildering variety of statements that could be reduced to the following list of hypotheses that have not yet been substantiated within anything approaching a reasonable degree of medical certainty with regard to the pathogenesis of autism. The fabric of this section is almost entirely speculative and, in most instances, is entirely discountable as the pathogenesis of autism. These unproven "alternative views" that may be rejected upon the basis of current scientific understanding are the following:

    a. Genetic disturbances lead to susceptibility to environmental influences that combine with developmental vulnerability of the nervous system that result in autism.
    b. The statement that regressive symptoms may be documented by video is not relevant to the argument stated above. Such documentation, which is indeed available in some instances, is not proof of the hypothesis. Documented degeneration may be seen in genetically determined regression such as is found in Rett syndrome and likely represents a different kind of vulnerability: it is a failure of continued genetically predetermined development of the nervous system at some "switching point" of gene activation. Such an event is well known to occur in infants who experience perinatal large vessel strokes. The hemiparesis that results from such strokes is not evident as a newborn. It appears in several months, the likely but as yet incompletely proven explanation of which is that it appears at a time when motor programs are relocated to cortex rather than deep within the brain.
    c. The second paragraph may or may not be true. As discussed above, there is no credible evidence to support the emotionally charged unproven statement that there has been a "drastic rise" in autism.
    d. The next paragraph has the same problems as the preceding paragraph. One could add that the genetic aspect considered in this section is reduced to one unproven concept: increasing vulnerability to environmental toxins. This grossly overlooks the considerable work that has been accomplished on genetic mechanisms that may play a role in autism—there are currently in excess of 1180 papers in the CPRL concerning the genetics of autism.
    e. The relationship of environmental exposure to "neurodevelopmental disorders" has been demonstrated including the results of intrauterine exposure to enormous amounts of

methylmercury in the Minimata Bay disaster. This was in part the result of concentration of the toxin in the fetus and the result included fetal death or severe static encephalopathies that could not in any way be mistaken for autism. On the other hand, considerable exposure to quantities of organic mercury in doses far in excess of the amount contained in vaccines – such as the carefully documented Seychelles mercury intoxication or for that matter contained in tooth fillings – have not been shown to be epidemiologically linked with the development of autism.

f. Elevated mercury levels in children with autism, discussed in the next paragraph, are not documented by laboratories certified with regard to methodology, reproducibility, and integrity of results such as are found in reputable hospitals. They are found by laboratories that are not willing to subject themselves to the scrutiny of agencies that certify the quality of laboratory results ensuring accuracy within the usual standards of the established medical community. Nor is there such authentication of the putative results of chelation for mercury in children with autism. Mercury level elevations in children may be found by established and bonded laboratories, but the manifestations found in such intoxicated children are not those of autism.

g. In the same paragraph, it is appropriate to endorse the fact that papers within the CPRL have investigated issues related to oxidative pathways, glutathione, folate, and other pathways that may be pertinent to vulnerability to neurological disease in relation to environmental exposure to toxins. This work is in its infancy and has not yet provided a body of information that supports a credible pathogenesis of autism. It is incorrect to state that there is conclusive laboratory evidence in children to support this mechanism. The only observations in children that can be made about this possible explanation of vulnerability to toxins are entirely by indirect measures, with results that can be inconclusively interpreted. The available information is entirely in experimental animals and involves the as yet quite uncertain determination of how one proves that behavioral abnormalities observed in such experimental animals are actually autism. The most conclusive feature observed in human autism is disturbance of communication, which cannot in any considerable degree be ascertained in laboratory rats. The remainder of this paragraph is purely speculative and without any convincing clinical or experimental validation in the CPRL.

h. The paragraph concerning association of gastrointestinal and immunological defects suffers from the same problems that are noted in the analysis of Yates' clinical course. Within a reasonable degree of medical certainty, there is no conclusive evidence to link these perceived problems, which are not commonly diagnosed in children with autism even when careful histories are ascertained. The "significant gastrointestinal pathology" derives from studies in Britain that have been thoroughly discredited methodologically and because of evidence for unethical behavior on the part of investigators.

i. The statement that "real change" and hope can be provided by acceptance of these various unproven hypotheses has often been cited in the history of medicine by individuals who have approached autism and other tragic disorders as opportunities to provide various costly services of unproven benefit, and that appear to many individuals dedicated to investigating the actual pathogenesis of these disorders as providing false hope, and in some instances, subjecting children to interventions, such as chelation, that are both painful and dangerous.

6. "Where is the lesion": The first paragraph manifests the same flawed formulation already discussed. Recurrent infections by no means imply an impaired immune system, for which there is no definite evidence in the case of this child. It is incorrect to imply that neurological problems can readily be localized in such a complex disorder as autism. In fact, the medical literature is littered with

assumptions about localization and pathogenesis of autism that, upon further investigation, have proven to unworkable or wrong. Generally, such approaches have been undertaken without the essential step of analyzing brain tissue of affected individuals. The discussion of various brain regions in this section, and their possible contributions to the disturbances found in autism, is in large measure speculative and does not reflect recent important advances in understanding the localization of some aspects of dysfunction in children with autism. In fact, this section has bits and pieces of the various speculations of the past 30 years, many of which now have little relevance to increasingly refined understandings of the pathology found in brains of individuals with autism.

It is not true to state that "any and all parts of the brain can be involved in autism…" Such a statement reflects inadequate perusal of the literature. The etiologic categories selected to represent the possible etiologic categories for autism also reflect inadequate depth of analysis of the available literature and appear in fact to set up "straw men" for the purposes of placing the novel hypothesis in a more favorable light.

7. "What is the Time Frame": There is inadequate documentation in the medical record for the 12-18 month period of regression. What follows in this section is a repetition of much of the information already considered. It is incorrect to state that, in "genetic-metabolic conditions," a proven genetic mutation is found. To the contrary, it is likely that there are a number of unknown genetic abnormalities that will account for the phenomenon of autism, whether or not associated with metabolic disturbances. The best model available is that of Rett syndrome, the genetic abnormality of which was characterized only relatively recently. This disorder has much in common with regressive autism: loss of language among the most important features. On the other hand, conditions that arise as the result of environmental toxins have little in common with autism, although there may be some features that without close inspection might be thought to represent autistic features.

8. "Differential Diagnosis and Discussion": This section repeats much that has been said or implied in the foregoing discussion and seems not, in any measurable way, to advance or provide a convincing argument for Dr. Corbier's novel hypothesis. The bulleted points at the bottom of page twelve are particularly troubling. It is not clear what is meant by the first point. Autism is typical of itself, the features repeating themselves with striking similarities. It must be differentiated from "atypical forms of autism" one must agree. It must be agreed that autism is a complex disorder and it should be approached as such. In my opinion, the problem with the chain of hypotheses expressed in Dr. Corbier's report is that it is a nontechnical analysis that stitches together a series of "causes" for which there is little evidence in the medical record, and for which no coherent biological support is advanced. There is no support for this hypothesis in the CPRL. In my opinion, based upon 30 years in clinical medicine and research science, I would designate the discussion philosophical rather than medical or scientific.

   The disorders of the autistic spectrum arise from various pathogenic pathways (Dr. Corbier has written "common clinical pathways" the meaning of which is quite unclear to me). This is because many different pathways have already been shown to produce autistic features, and that is exactly why the spectrum is heterogeneous. However, regressive autism exhibits a fairly characteristic course, the manifestations of which share "much of a muchness." Because of this comparative uniformity of phenotype, it is likely that a unifying underlying pathogenesis will be identified, most likely genetic. Strong evidence for this basis to regressive male autism is the resemblance of the clinical course of digression and the development of electroencephalographic abnormalities to Rett syndrome, a known genetic cause of a regressive form of autism in girls.

The final bullet in this section is another hypothesis unsupported by a balanced appraisal of the available data in CPRL. It repeats the unproven hypothesis that "environmental changes and practices" help explain the unproven "increased incidence of autism." Repetition of these assertions does not make them valid. There is no solid evidence yet for these hypotheses. The argument is broadened rather remarkably to include rising prevalence for diabetes (for which there is solid evidence and several important, if as yet unproven, unifying hypotheses in explanation) and "bipolar disorder." A lengthy discussion could be directed at this offhand observation, but it falls outside of the scope of this discussion. That heterogenous diagnostic entity may or may not have increased in incidence. Many believe that that too represents a pseudo-epidemic; the result of changes in style of labeling. The remainder of the bullets merely repeat as yet unproven assertions already considered in this analysis.

9. "Genetic, epigenetic and non genetic factors": This section contains a review in greater detail of Dr. Corbier's hypotheses concerning the pathogenesis of Yates' autistic regression within the setting of genetic diseases. Of greatest importance is the fact that Dr. Corbier apparently accepts the notion that Yates' condition is "very likely" related at least in part to one or more genetically determined processes, with which I agree. I do not agree that other influences are required.

10. "Central nervous system infections…": This section contains a review in greater detail of Dr. Corbier's hypotheses concerning the pathogenesis of Yates' autistic regression within the setting of infectious or inflammatory processes. This discussion relied heavily on papers found in the CPRL, but whose validity have been intensely scrutinized with serious concern over methods and non-scientific influences that suggest the observations are likely to be invalid. Questions of a serious nature have been raised concerning the ethical standards of some individuals engaged in this research. The likely invalidity of these findings is a position with which I agree. Particularly troubling in this section is the hypothesis that developmental consequences (e.g. autism) represent other forms of measles virus persistence within the central nervous system, alongside the known encephalitic or postinfectious conditions that have been well-characterized in the CPRL. There is no support for this hypothesis in the available CPRL. This is a subject that has been investigated extensively with regard to multiple sclerosis and has proven to be an invalid hypothesis. The same statement can be said once again concerning the "cumulative insult" theory that Dr. Corbier posits.

11. "A toxicological condition": The issues raised in this section contain hypotheses already referred to in the discussion above. Although important studies of the toxic effects of mercury are cited, it is important to make clear that these studies either report toxic effects that are quite distinct from those observed in autism (e.g. Minimata Bay disease) or fail to support the view that there is any epidemiological confirmation that chronic low dose mercury produces autism. Dr. Corbier reverts to the "cumulative insult" theory to explain why some individuals develop autism from "low dose mercury." Once again, on balance, there is no support for this theory in the CPRL, and the theory itself has, in my view, not been validated scientifically. Rather, it remains a hypothesis. I state these conclusions with a reasonable degree of medical certainty.

The conclusions of Dr. Corbier's report reiterate the hypotheses already noted, and his conclusion that vaccination or mercury toxicity accounts for Yates' development of regressive autism is not supported by reliable scientific evidence.

Sincerely,

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