because it could help displace the goal-less, progress driven, never-happy medicine that grew out of [its] embrace of modernism." We need to understand "the social meaning of medicine and health care," he declared, "and the relationship of medicine to the cultures of which it is a part." In this regard, J. Kirby[10] of Australia also made some relevant comments (concerning the need to slow the headlong rush of modern medicine),

"My hope is that it won't be the epitaph of our generation that people will say: 'Here was a community which developed the most amazing, dazzling fields of science and yet proved themselves so indifferent or incompetent, that they didn't address the serious social and ethical consequences of what they were up to.'"

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Thimerosal and Autism?

Concern has been expressed over the possibility that the mercury-containing compound thimerosal in vaccines may cause autism.[1–4] Thimerosal is sodium ethylmercury thiosalicylate, an organic compound of ethyl mercury, included in certain vaccines to protect multiple dose ampules from bacterial and fungal contamination. Mercury in sufficient dose is neurotoxic, and probably more toxic in the immature brain. It is reasonable to ask whether thimerosal in childhood vaccine increases risk of chronic childhood neurologic disability and specifically of autism. The available data with which to address the question are very limited and largely inferential. Most of the information we have about mercury toxicity is related to exposure to methyl rather than ethyl mercury.

Bernard et al[1] offered an hypothesis that autism is an expression of mercury toxicity resulting from thimerosal in vaccines. They base this hypothesis on their views[2] that the clinical signs of mercury toxicity are similar to the manifestations of autism, that the onset of autism is temporally associated with immunization in some children, that the recent increase in diagnosis of autism parallels exposure to thimerosal, and that there are higher levels of mercury in persons with than without autism.

This review will examine these issues and others to ask whether, according to evidence now available, thimerosal is a probable cause of autism. We will not discuss which, if any, of the differing guidelines designed to limit exposure to mercurials is appropriate for deciding whether thimerosal in vaccines is in all regards safe for children. Our focus is on a narrower but important question: whether current evidence indicates that mercury at any known dose, form, duration, age, or route of exposure leads to autism.

ARE THE CLINICAL MANIFESTATIONS OF AUTISM SIMILAR TO THOSE OF RECOGNIZED MERCURY TOXICITY?

Bernard et al[1] present a table listing ~95 clinical findings they consider to be shared by autism and mercury poisoning. Their table does not distinguish typical and characteristic manifestations of either disorder from the rare, unusual, and highly atypical.

In mercury poisoning, the characteristic motor findings are ataxia and dysarthria (Table 1).[5,6] These signs, along with tremor, muscle pains, and weakness, are noted on relatively high-dose exposure, acute or chronic. In 3 Romanian children accidentally exposed to ethyl mercury in a fungicide, these same symptoms were prominent.[7] The outcome of fetal methyl mercury poisoning in severe form also included spasticity.[8] In contrast, in autism, the only common motor manifestations are repetitive behaviors (stereotypies) such as flapping, circling, or rocking. Persons with Asperger syndrome may be clumsy, and hypotonia has been noted in some infants with autism; the frequency of clumsiness and hypotonia in autism spectrum disorders is not established. No other motor findings are common in autism, and indeed the presence of ataxia or dysarthria in a child whose behavior has autistic features should lead to careful medical evaluation for an alternative or additional diagnosis.

The most characteristic sensory finding of mercury poisoning is a highly specific bilateral constriction of visual fields.[5,6,9] With lesser exposure there may be compromise of contrast sensitivity.[10,11] In addition, there may be paresthesias or, in infants, erythema and pain in hands and feet because of peripheral neuropathy. In autism, decreased responsiveness to pain is sometimes observed along with hypersensitivity to other sensory stimuli, including hyperacusis. The "sensory defensiveness" of autism seems to reflect altered sensory processing within the brain rather than peripheral nerve involvement.[12–14]

Received for publication Dec 2, 2002; accepted Dec 2, 2002.
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TABLE 1. Characteristic Findings in Autism and in Mercury Poisoning

	Autism	Mercurism
Motor	Stereotypies	Ataxia, dysarthria
Vision	No abnormality	Constricted visual fields
Speech	Delay, echolalia	Dysarthria
Sensory	Hyper-responsiveness	Peripheral neuropathy
Psychiatric	Socially aloof, insistence on sameness	Toxic psychosis; in mild cases, nonspecific depression, anxiety
Head size	Large	Small

Other signs that may appear in children with chronic mercury toxicity, such as hypertension,[15] skin eruption,[16] and thrombocytopenia,[17] are seldom seen in autism.

In relatively mild mercurism in persons without characteristic motor or sensory changes, psychiatric symptomatology may be absent, and if present is nonspecific, with findings such as depression, anxiety, and irritability.[18–20] There may be impairment of recent memory. Even for individuals with known elevated postmortem levels of mercury in brain, it may be impossible to conclude whether the nonspecific psychiatric findings they demonstrated in life were the result of mercury toxicity.[21]

When severe mercury poisoning occurs in prenatal life or early infancy, head size tends to be small and microcephaly is common.[22] Prenatal exposure to other neurotoxins—lead, alcohol, and polychlorinated biphenyls, for example—also predispose to decreased head size. In contrast, in autism increasing evidence indicates that head size[23–25] and, as measured by volumetric magnetic resonance imaging, brain size[26,27] tends to be larger than population norms.

At sufficient dose mercury is indeed a neurotoxin, but the typical clinical signs of mercurism are not similar to the typical clinical signs of autism.

ONSET OF AUTISM SYMPTOMS AFTER IMMUNIZATIONS

Evaluation of causation cannot depend on temporal association as reflected by anecdotal observations of selected instances in which a relatively uncommon outcome such as autism is noted after a common childhood exposure such as immunization. Only rigorous methods that attempt to include all instances of both exposure and outcome can provide evidence of association, and association is necessary but not sufficient to establish causation.

Age of onset of symptoms can be highly misleading as an indicator that some environmental event has caused or precipitated a disorder. Even single gene disorders may have a period of apparently normal development (~1.5 years in Rett syndrome, 45 years in Huntington's chorea) before symptoms begin. The onset of clinically recognizable signs and symptoms in Rett and Huntington syndromes does not require an environmental "second hit." In Rett syndrome, the mutation causes previously apparently normal children to lose acquired developmental milestones after 1 years old to 2 years old, with a phase during which they may present behaviors consistent with autism. This disorder can also have its clinically apparent onset soon after the completion of immunizations, but Rett syndrome is known to be determined by a single genetic mutation that produces failure in the normal program of brain development. If we did not understand its genetic basis, we might suspect that Rett syndrome was attributable to environmental factors including immunization. The situation for autism is still unknown, but the onset of signs in the second year of life does not prove (nor disprove) a role for environmental factors in etiology.

INCREASE IN DIAGNOSIS OF AUTISM IN PARALLEL WITH INTRODUCTION OF MERCURY-CONTAINING VACCINES

There has clearly been a broadening of the criteria for autism, better case-finding, increased awareness by clinicians and by families, and an increase in referrals of children for services as it has become recognized that early treatment improves life for the child and family.[28,29] Whether the sum of these is sufficient to account for the more frequent diagnosis of autism is a matter of contention and is properly settled by careful research.

If, for the sake of discussion, we assume there was a true increase in the occurrence of autism in the 1990s, is exposure to thimerosal the only or the best hypothesis to explain the increase? There have been many changes in life in industrialized countries during the last decades, including changes in many environmental exposures and aspects of medical care that could be considered for their biological plausibility as contributors to autism occurrence or severity.

MERCURY LEVELS IN AUTISTIC PERSONS

Bernard et al[2] state that "elevated mercury has been detected in biological samples of autistic patients," but unfortunately do not provide references. Aschner and Walker[30] found no paper published in the peer-reviewed literature that reported an abnormal body burden of mercury, or an excess of mercury in hair, urine, or blood. The one paper that sought a relationship between autism and mercury levels in hair did not observe such an association.[31] We did not find evidence that chelation therapy has led to improvement in children with autism.

NEUROPATHOLOGY

A substantial literature describes the neurotoxicity of methyl mercury but relatively little is known about the impact of ethyl mercury on the nervous system, especially with repeated low-dose exposure.

The passage of methyl mercury across the blood-brain barrier is facilitated by an active transport mechanism, whereas the passage of ethyl mercury into the brain does not have such a transport system and is further hindered by its larger molecular size and faster decomposition.[32] At equivalent doses, higher levels of mercury have been found in the blood and less in brain following administration of ethyl mercury than methyl mercury.[33] These findings support the observation that the risk of toxicity from ethyl mercury is overestimated by comparison with the risk of intoxication from methyl mercury.[34] Ethyl mercury exposure has been reported to be more likely than methyl mercury to produce lesions of the spinal cord, skeletal muscle, and myocardium.[8]

The effects of mercurial compounds are influenced by dose and duration of exposure and by maturational stage.

Studies in experimental animals exposed postnatally to ethyl mercury indicate patchy damage in the cerebellar granule cell layer, while methyl mercury produced a diffuse abnormality.[35] Methyl mercury exposure has been reported to disrupt neuronal migration primarily in the motor cortex[36] and in the cerebellar granule cell layer.[37] In humans with massive exposure to mercurials resulting in death, brains showed severe atrophy and gliosis of calcarine cortex, as well as diffuse neuronal loss and gliosis of the auditory, motor and sensory cortices, and extensive cerebellar atrophy.[38]

The most extensive pathologic studies of the brain in mercury poisoning followed methyl mercury exposure resulting from contaminated seafood in Japan and from contaminated bread in Iraq. Microscopic findings in these brains included decreased numbers of neurons and increased numbers of glial cells and macrophages throughout the cortex, as well as loss of granule cells and irregularity of the Purkinje cell layer in the cerebellum. In 2 Iraqi infants exposed prenatally to methyl mercury there was a simplified gyral pattern, short frontal lobe, and reduction in white matter volume, along with derangement and lack of definition of the cortical layers and heterotopic neurons in cerebrum and cerebellum.[39]

Thus, in both prenatally and postnatally exposed brain, methyl mercury resulted in neuronal cell loss and increased gliosis in the cerebral cortex, in some adults marked atrophy of the calcarine cortex, and atrophy of the cerebellum with consistent loss of granule cells and relative sparing of Purkinje cells. The weight or volume of the mercury-exposed brains has not been presented, but the atrophy associated with neuronal loss and in the infant cases the reduced white matter volume suggest that these brains were likely to be reduced in size.

In ethyl mercury toxicity in children, nerve cell loss was widely present but most marked in calcarine cortex, and there was diffuse proliferation of glia, demyelination of ninth and tenth cranial nerve roots, and atrophy of the cerebellar granule cell layer with relative sparing of Purkinje cells.[8]

In contrast, examined at autopsy, brains of autistic persons are commonly enlarged both by weight[40] and volume.[26] Larger head circumference and enlargement seen on volumetric magnetic resonance imaging studies in autism have been noted above. There have been no reports of significant cerebral cortical neuronal loss or calcarine atrophy in autism. The most frequently reported findings in the autistic forebrain have been unusually small, closely packed neurons and increased cell packing density in portions of the limbic system, consistent with curtailment of development of this circuitry.[40]

Age-related abnormalities have been observed in the deep cerebellar nuclei and inferior olivary nucleus of the brainstem in autism. The most consistent finding in the neuropathology of autism is reduction in Purkinje cells in the cerebellum, primarily in the posterior inferior hemispheres.[41–43] Involvement of granule cells has rarely been reported. In contrast, mercury-exposed brains have shown significant and consistent damage to the cerebellar granule cell layer with relative preservation of Purkinje cells.

Thus, there seem to be major differences in the neuroanatomic findings in autism as compared with those in mercury toxicity.

IN HUMAN POPULATIONS EXPOSED TO MERCURY, DID AUTISM INCREASE?

In the first half of the 20th century, mercury was a constituent of medications administered to treat worm infestations and teething pain. Use of these compounds was associated with illness in young children, affecting chiefly those 8 months old to 2 years old. These infants showed photophobia, anorexia, skin eruption, and bright pink color of hands and feet, which peeled and were painful.[44] This condition, called "pink disease" or acrodynia, was relatively common, and the cause of 103 deaths in England and Wales in 1947.[45] Survivors were not described to have behavioral disorders suggestive of autism.

In the 1950s in Minamata and in the 1960s in Niigata, Japan, there were epidemics of methyl mercury poisoning resulting from discharge of industrial wastes into coastal waters, with consumption of contaminated fish by humans. Heavy prenatal exposure resulted in low birth weight, microcephaly, profound developmental delay, cerebral palsy, deafness, blindness, and seizures.[6,46] Affected adults experienced impairments of speech, constriction of visual fields, ataxia, sensory disturbance, and tremor.

Was autism recognized with higher frequency in Japanese children in the period of these toxic outbreaks or soon after it, especially in those born in the regions affected by the tragic poisonings? Japanese reports in the English language do not indicate that Japanese clinicians thought so. Comparable in earlier periods, the rates of autism were higher as reported in Japan in the 1980s than in studies from other countries.[47–49] This difference was attributed by Japanese authors to broader diagnostic criteria and excellent ascertainment.[50] Definitions and methods of ascertainment were widely different in different studies, so comparisons are difficult. A study in Fukushima-ken[51] is described here in some detail because it provides an example of the issues faced by studies of prevalence during this period and includes

an analysis by year of birth in an area not far distant from Niigata. In this study, conducted in 1977, the authors attempted to evaluate all children with autism 18 years old or less who were born in the province in 1960 through 1977. They ascertained cases by sending a letter and questionnaire to 2233 institutions to find children with "autistic behavior," not further defined. Responses were received from 72.6% of the institutions, which covered 38% to 40% of children in the province. How responding institutions differed from those not responding is not stated. The autism prevalence estimates reported included children in the responding institutions in the numerator, and all children in the area in the denominator. If the nonresponding institutions had affected children in their care, and if there were changes over the period of the study that might influence recruitment of affected children at competing institutions, such changes could markedly influence the result. Based on their final diagnosis, there were more children with "autistic mental retardation" than with "early infantile autism," but no information is provided on the basis for this distinction, nor on birth year patterns for the former group.

The authors of the Fukushima-ken study[51] reported higher rates of autism in children born between 1966 and 1974 than in births 1960 through 1965 or after 1975. The authors considered that the reason for the lower rates of autism in children born before 1966 "was probably that autistic children had become older, lost the unique feature[s] of young autistic children and had been overlooked." This suggests that procedures for locating older subjects and criteria for diagnosis were not appropriate for all of the wide age span evaluated. For children born in the last years of the study, the low rates of autism surely entail severe undercounts as these children were 3 years old or less at the time of ascertainment. Although this study might have tested the question as to whether autism was more frequent near to outbreaks of mercury poisoning, methodologic problems potentially invalidate the time trend analysis, and the short follow-up for the most recent birth years means that no conclusions can be drawn regarding children born 1974 or later.

Studies that followed victims of high-dose acute or chronic mercury poisoning resulting from contaminated foods in Iraq, Pakistan, Guatemala, and Ghana have not reported manifestations suggestive of autism in survivors. In contrast, many of these survivors had clinical signs such as persisting ataxia and dysarthria that are seldom seen in autism.

An unpublished retrospective study was noted by the Institute of Medicine's Immunization Safety Review Committee.[52] As described in a Canadian Communicable Disease Report,[53] this study examined 10 years of data from a large database derived from 7 health maintenance organizations that covered ~2.5% of the United States population. A weak but statistically significant (relative risk ratio <2.0) association was found between measures of cumulative exposures to thimerosal and the presence of speech delay and attention-deficit/hyperactivity disorder, but not autism. There were many limitations of this analysis and its ability to identify bias and confounding. A second unpublished screening study did not confirm the findings of the first. Although far from definitive, these studies represent the only direct investigation to date of a possible association of thimerosal exposure with autism. Neither study observed such an association.

Two studies have examined neurologic and psychologic function in young children associated with lower dose but repeated dietary exposure to methyl mercury. In the Faeroe Islands, exposure was via consumption of marine fishes and mammals (whales). In the Faeroes, there may have been additional toxins including polychlorinated biphenyls and perhaps others.[54,55] The Faeroe study of 428 to 900 children at 7 years old observed an association of mercury levels in cord blood or maternal hair with impaired performance in tests of attention, memory for visuospatial information, the Boston Naming Test, fine motor function, and verbal learning.[56,57] In contrast, in the Sechylles study of >700 children, exposure was to marine fish only, and boys with higher levels of hair mercury performed better on some tests, including the Boston Naming Test and 2 tests of visual motor coordination.[59,60] The authors considered their enhanced performance might be related to beneficial effects of constituents other than mercury in fish. Myers et al[54] have discussed sources of difference in the results of these studies.

The Faeroe and Seychelles studies were probably large enough to detect a substantial but not a minor increase in autism, if it was present. Neither study was designed to investigate an association of mercury exposure with autism, but autism in all but its milder forms produces fairly striking behavioral aberration in young children. Were the endpoints examined appropriate for identification of children with autism? The Faeroe study included little behavioral assessment. Based on experience in lead toxicity studies, the Seychelles study used the Child Behavior Checklist overall rating at 66 months and 96 months. Testing at 66 months included Checklist subscales related to withdrawal, anxiety, and problems in social function, attention, and thought. The Child Behavior Checklist is not ideally sensitive for recognition of autism, but would probably identify the majority of affected children.[60] Myers et al,[54] reviewing nearly 50 years of research on mercury exposure and 27 years experience in human neurotoxicity of methyl mercury, concluded, "Our research has not identified any adverse associations between [methyl mercury] exposure from fish consumption and clinical symptoms or signs."

CONCLUSION

Thimerosal is being eliminated from the vaccines used in routine infant immunization programs in the United States and Canada. If thimerosal was an important cause of autism, the incidence of autism might soon begin to decline. One can hope but not expect that that will happen; time will tell.

Mercury poisoning and autism both affect the central nervous system but the specific sites of involvement in brain and the brain cell types affected are

different in the two disorders as evidenced clinically and by neuropathology. Mercury also injures the peripheral nervous system and other organs that are not affected in autism. Nonspecific symptoms such as anxiety, depression, and irrational fears may occur both in mercury poisoning and in children with autism, but overall the clinical picture of mercurism—from any known form, dose, duration, or age of exposure—does not mimic that of autism. No case history has been encountered in which the differential diagnosis of these 2 disorders was a problem. Most important, no evidence yet brought forward indicates that children exposed to vaccines containing mercurials, or mercurials via any other route of exposure, have more autism than children with less or no such exposure.

Continuing vigilance is necessary regarding the safety of vaccines, as is open-minded evaluation of new evidence. However, such evidence must be of sufficient scientific rigor to provide a responsible basis for decisions that influence the safety of children. When information is incomplete, as it is at present for thimerosal-autism questions, a balancing must be made of risks posed by vaccine constituents and the benefits of disease prevention achieved by keeping immunizations widely available. On the basis of current evidence, we consider it improbable that thimerosal and autism are linked.

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Medical Information Systems in Pediatrics

The safety, effectiveness, impact, and risks of medical information systems have received little attention from clinical investigators in pediatrics. Krishna and colleagues'[1] study of the impact of a multimedia asthma education program published in this issue of *Pediatrics* is an exception to this observation and a wonderful example of a clinical research study on the effects of a medical information system.

Information systems that collect, process, and disseminate medical information are ubiquitous in our practice of pediatric medicine. These information resources serve a variety of functions, but they all have 1 thing in common: they are being used in a high-stakes environment. Technical glitches such as programming errors,[2] hardware malfunctions, communication failures, and data corruption or data loss can endanger the well-being of our patients. Human-machine interface errors like inappropriate use (a program designed for adults used in pediatrics), incomplete or inaccurate data entry, rearranged physician priorities, and the generation of false expectations and overreliance (the program will tell me when I made a mistake) all may lead to medical errors and subsequently to morbidity and mortality.

Despite their increasing presence, relatively little effort has been undertaken to systematically gather evidence on the safety and efficacy of medical information systems used with pediatric patients. Information systems used in pediatrics are fundamentally different from adult systems. They must handle weight-based dosing, different history components (such as development), monitor growth based on age, and if targeted for use by a child, must be designed to be child-friendly in language and graphics.

In April 2002, the Bush Administration decided to retain a 3-year-old rule that gives the Food and Drug Administration power to demand that pharmaceutical companies conduct targeted studies to learn about medication side effects and set proper doses for children.[3] Linked to an incentive program by Congress, this "pediatric rule" has generated evidence on particular pediatric risks as well as pediatric-specific metabolism.

Medical information systems are burdened with inherent danger in conjunction with pediatric-specific risks as well as significant expenses. In the best interest of our patients, pediatricians should lobby for an extension of the "pediatric rule" to information systems in pediatric settings. I applaud *Pediatrics* for providing a forum for evidence-based pediatric medical informatics.

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Received for publication Dec 19, 2002; accepted Dec 19, 2002.
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Pediatrics 2003;111;674
DOI: 10.1542/peds.111.3.674

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