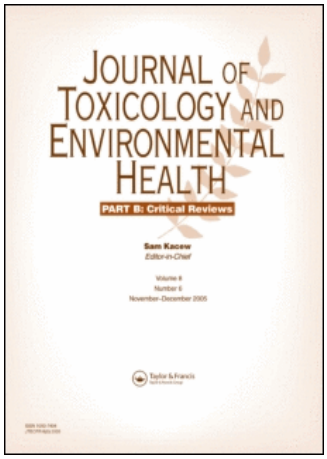

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A Review of Thimerosal (Merthiolate) and its Ethylmercury Breakdown Product: Specific Historical Considerations Regarding Safety and Effectiveness

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A REVIEW OF THIMEROSAL (MERTHIOLATE) AND ITS ETHYLMERCURY BREAKDOWN PRODUCT: SPECIFIC HISTORICAL CONSIDERATIONS REGARDING SAFETY AND EFFECTIVENESS

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Thimerosal (Merthiolate) is an ethylmercury-containing pharmaceutical compound that is 49.55% mercury and that was developed in 1927. Thimerosal has been marketed as an antimicrobial agent in a range of products, including topical antiseptic solutions and antiseptic ointments for treating cuts, nasal sprays, eye solutions, vaginal spermicides, diaper rash treatments, and perhaps most importantly as a preservative in vaccines and other injectable biological products, including Rho(D)-immune globulin preparations, despite evidence, dating to the early 1930s, indicating Thimerosal to be potentially hazardous to humans and ineffective as an antimicrobial agent. Despite this, Thimerosal was not scrutinized as part of U.S. pharmaceutical products until the 1980s, when the U.S. Food and Drug Administration finally recognized its demonstrated ineffectiveness and toxicity in topical pharmaceutical products, and began to eliminate it from these. Ironically, while Thimerosal was being eliminated from topicals, it was becoming more and more ubiquitous in the recommended immunization schedule for infants and pregnant women. Furthermore, Thimerosal continues to be administered, as part of mandated immunizations and other pharmaceutical products, in the United States and globally. The ubiquitous and largely unchecked place of Thimerosal in pharmaceuticals, therefore, represents a medical crisis.

Thimerosal (Merthiolate) is an ethylmercury-containing pharmaceutical compound that is 49.55% mercury and that was developed in 1927. Thimerosal continues to remain a part of the modern practice of medicine and a part of modern vaccines to this day. For decades Thimerosal has been marketed as an antimicrobial agent in a range of products, including as topical antiseptic solutions and antiseptic ointments for treating cuts, nasal sprays, eye solutions, vaginal spermicides, diaper rash treatments, and perhaps most importantly as a preservative in vaccines and other injectable biological products, including Rh_o(D)-immune globulin preparations, despite evidence, dating to the early 1930s, indicating Thimerosal to be potentially hazardous to humans and ineffective as an antimicrobial agent. Unchallenged, it remained in U.S. pharmaceutical products until the 1980s when Thimerosal began to be withdrawn because of its demonstrated infectiveness and toxicity in topical pharmaceutical products. Ironically, while Thimerosal was being eliminated from topicals, it was becoming more ubiquitous in the immunization schedule for infants and pregnant women.

The removal of Thimerosal from several childhood vaccines and Rh_o(D) injections was not completed in the United States until after the turn of the 21st century, and today Thimerosal remains in numerous prescription and over-the-counter pharmaceutical products (Subcommittee on Human Rights and Wellness, 2003) and the influenza vaccine, now routinely recommended for administration to infants and pregnant women (Advisory Committee on Immunization Practices, 2006).

Recent statements made by those holding national and global responsibility for vaccine safety are difficult to reconcile with the known and published toxicity of Thimerosal and ethylmercury. For example, Francois et al. (2005) from the World Health Organization (WHO) and the U.S. Centers

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for Disease Control and Prevention (CDC) reported, "Thimerosal (or thiomersal) has been used for a long time as an effective preservative in some vaccines, and a number of pharmaceutical and cosmetic products. It has both bactericidal and fungicidal properties and has effectively been applied to prevent contamination of opened, multidose containers . . . Thimerosal has been used for >60 years in infant vaccines and in other applications and has not been associated with adverse health effects in the general population . . . Hence there is no stringent reason to stop the use of Thimerosal-containing vaccines in current immunization programs worldwide. The balance of risks and benefits of these vaccines is very clearly positive" (p. 954–955).

Offit and Jew (2003), reported, "However, no data exist on the capacity of low-dose, chronic exposure to ethylmercury to harm the developing nervous system . . . Parents should be reassured that quantities of mercury . . . contained in vaccines are likely to be harmless on the basis of exposure studies in humans or experimental studies in animals" (p. 1395, p. 1399).

It appears that government regulators in many cases did not analyze the potential impact of mercury upon the fetuses and infants who were being exposed. In fact, alarmingly, they were not even responsible for initially calculating the cumulative amount of mercury contained in the immunization schedule. This article is a historical review of the literature concerning Thimerosal and its ethylmercury breakdown product.

EARLY HISTORY OF THIMEROSAL

Kharasch (1928) of College Park, MD, working in collaboration with Eli Lilly and Company (Lilly) at the University of Maryland, filed a patent for an alkyl mercuric sulfur compound in Indianapolis, Indiana. In his patent Kharasch claimed that compounds such as Thimerosal were, "well-suited for intravenous injection . . . [and] effective therapeutically as germicides." Shortly thereafter, with the declaration that Thimerosal was "well-suited" for administration to humans and "effective" as a germicide, Lilly began to manufacture and market this new product.

Kharasch's assertion of Thimerosal's benign and therapeutic nature was merely the beginning of its scientific assessment. Smithburn and his colleagues (1930) recorded observations made during human clinical experiments using Thimerosal to try to treat meningitis victims. In this article, they noted, "the treatment has remained essentially the same throughout the epidemic" (p. 779). Smithburn and his colleagues (1930) then described the use of Thimerosal in an experimental effort to treat the disease. Specifically, they stated, "Intravenous administration of antiseptic solution was tried and found wanting despite the in vitro activity of the agent" (p. 779). Smithburn and his colleagues (1930) also reported that efforts were made to combat positive nasopharyngeal cultures with Thimerosal. They detailed a procedure to address this source of infection, applying ephedrine sulfate in each nostril followed by Merthiolate (1 part per 4000 strength) twice daily. It was noted that, after the institution of this therapy, no nasopharyngeal cultures were positive. However, Smithburn et al. (1930) also noted that the treatment was "symptomatic."

In light of the preliminary research upon Thimerosal, early concerns were raised about Thimerosal: "in view of our experience with the Merthiolate solution, we have to know pretty definitely what to expect from Merthiolate ointment and jelly before they are put on the market" (Subcommittee on Human Rights and Wellness, p. 58). It was felt, "Our experience with the solution ought to serve as a warning and certainly in the face of that warning we ought not to advocate the use . . . without some pretty definite evidence that we will not repeat our solution experience" (Subcommittee on Human Rights and Wellness, p. 58).

Despite the concern, Powell and Jamieson (1931) subsequently noted, regarding the toxicity of Thimerosal, "Toxicity in man. Merthiolate has been injected intravenously into 22 persons in doses up to 50 cubic centimeters of 1% solution . . . The toleration of such intravenous doses indicates a very low order of toxicity of Merthiolate for man. This information has been supplied through the kindness of Dr. K.C. Smithburn of Indianapolis who has had occasion to use Merthiolate in a clinical way. Dr. Smithburn stated in these cases 'beneficial effect of the drug was not definitely proven. It did not appear, however, to have any deleterious action when used in rather large doses intravenously when all the drug entered the vein'" (p. 306).

These statements and conclusions by Powell and Jamieson (1931) have been cited over many decades, and continue to this day, to be cited in defense of the questionable claims that Thimerosal had a low potential toxicity in humans. Upon closer inspection, however, it is apparent that significant information regarding the clinical trial experience with Thimerosal was not published.

First, in their article, Powell and Jamieson (1931) failed to reveal that the subjects evaluated by Smithburn and his colleagues (1930) had, in fact, had meningitis, and were not healthy, a revelation that would have called into question Powell and Jamieson's conclusions regarding the nontoxicity of Thimerosal. It should be noted that Powell and Jamieson (1931) provided a table in which the 22 subjects injected with Thimerosal were identified. These subjects, based upon the information provided in the table, received massive doses of mercury from intravenous administration of Thimerosal. The table notes that approximately one-third of the patients were followed for only 1 d after the therapy. The table failed to note, however, that most probably this follow-up period was so short because these individuals died. The table also noted only one patient was followed for 62 d. This maximum follow-up length of 62 d was far too short to accurately discern any chronic damage produced by the mercury, because mercury toxicity manifests fully only several months after exposure. The study was also flawed because any neurological and/or other damage observed was likely attributed to the meningitis rather than the Thimerosal exposure. Additionally, Powell and Jamieson (1931) specifically commented that they evaluated patients, in particular, for shock or anaphylaxis-type immediate reactions to the administration of Thimerosal. It is important to note that these outcomes are not typical of mercury toxicity in humans.

Second, it is also apparent that Powell and Jamieson (1931) failed to emphasize their disturbing animal toxicity data. In fact, Powell and Jamieson (1931) had already determined that administration of low milligram doses of Thimerosal per kilogram body weight in several different animals was acutely toxic and resulted in significant numbers of animals dying within days of exposure.

Regarding the reported conclusions reached by Powell and Jamieson (1931), it was even commented that "Considering the type of patient involved, one might question these observations [the appearance of no deleterious action] as providing adequate indication of any harmful effects of high doses of Merthiolate in humans, in particular, more long term effects" (Subcommittee on Human Rights and Wellness, p. 58).

Kharasch (1932) filed a new patent application in an effort to acknowledge the potential dangers of the germicide/antiseptic he had developed. Kharasch (1932) stated in this second patent, "I will describe my invention more specifically in connection with that one of such compounds which is now in most general use. That is sodium ethyl mercuri-thiosalicylate, which is known on the market as Merthiolate." According to Kharasch (1932), when Thimerosal "is first made, it is entirely bland, both to the skin and mucous membrane. However, it is found that on standing . . . the solution loses its blandness and acquires certain burning properties; which make its use as an antiseptic and bactericide less desirable." In describing the chemical basis for Thimerosal's ability to acquire "certain burning properties," Kharasch (1932) detailed an important discovery regarding the decomposition products of Thimerosal. Kharasch (1932) recorded that if "such for instance as for sodium ethyl mercuri-thiosalicylate, is allowed to stand, there is a dissociation of a few of the molecules at the bond between the sulphur and the ethyl mercury radical, producing a small quantity of resultant ions" and that, "However, on account of the invariable presence of oxygen, and of a catalyst such as copper, the sulphur-containing ion. . .is oxidized to the di-thio compound . . . The formation of the di-thio compound removes these sulphur-containing ions from the . . . mixture . . . so that progressively more ionization of the alky mercuric sulphur compound occurs . . . This process results in an excess of the mercuri ions such as $C_2H_5–Hg^{++}$ —which react with the hydroxyl ions present in the solution to form $C_2H_5–Hg^{++}–^{-}OH$." Subsequently, Kharasch (1932) went onto describe in the patent that the $C_2H_5–Hg^{++}–^{-}OH$ breakdown product of Thimerosal might mediate adverse reactions in humans. These observations are important because they demonstrate knowledge that Thimerosal would break down, in fairly rapid order, to produce ethylmercury hydroxide and thiosalicylate, and that the ethylmercury breakdown product was the one mediating Thimerosal toxicity.

Nonetheless, Marks et al. (1932) from the Lilly Research Laboratories reported, "Merthiolate (sodium ethyl mercuri thiosalicylate), an organic mercurial compound, seems to fulfill the requirements of a satisfactory disinfectant . . . This compound has been shown to possess active germicidal properties, maintaining its effectiveness in the presence of media most nearly resembling the tissues, such as serum agar and white clot or fibrin agar. It is readily soluble, possesses definite penetration properties, and does not precipitate serum proteins. Merthiolate has a low degree of toxicity for animals and human beings, does not hemolyze red blood cells, and does not injure sensitive bacterial antigens and antibodies. It has been found to stimulate tissue cell growth and healing" (p. 443).

By the 1930s, Thimerosal was promoted for uses beyond topical antiseptic application. For example, Jamieson and Powell (1931) described Thimerosal as an efficient preservative in biological products.

While the applications for Thimerosal were increasing, Kharasch (1935) later applied for a third patent for "organo-mercuri-sulfur compounds." In this patent, Kharasch's acknowledgment of Thimerosal's ineffectiveness and adverse effects in clinical practice exceeds all of his previous statements: "It is the object of my invention to stabilize more effectively than has heretofore been done certain antiseptic and bactericidal . . . compounds, which without such stabilization tend to form disassociation products and to thereby both lose their effectiveness as antiseptic germicides and to develop certain medicinally undesirable properties."

In 1935, some of the first serious safety concerns were raised regarding Thimerosal. Specifically, researchers reported a "reaction in about 50% of the dogs injected with serum containing dilutions of Merthiolate, varying in 1 in 40000 to 1 in 5000, and we have demonstrated conclusively that there is no connection between the lot of serum and the reaction. In other words, Merthiolate is unsatisfactory as a preservative for serum intended for use on dogs." They also noted, regarding the reactions observed in dogs following administration of Thimerosal-containing serums, that "in some instances, the reaction is extremely severe." It was concluded, "I might say that we have tested Merthiolate on humans and find that it gives a more marked . . . reaction than does phenol or tricresol" (Subcommittee on Human Rights and Wellness, p. 34–35). Additionally, Salle and Lazarus (1935) determined that Thimerosal was 35.3 times more toxic for embryonic cells than for the bacterial cells that Thimerosal was supposed to kill.

Soon after this 1935 publication by Salle and Lazarus, Cummins (1937) documented in the literature the first reports of Thimerosal-induced poisonings in animal model systems. Specifically, he described, "two sets of 7 flasks each were treated with an amount of Merthiolate varying in dilution from 1 to 100 to 1 in 10 million of the medium in each series. . . The guinea-pigs inoculated with 1 c.cm. of the mixtures after 24 hours all died; the first of Merthiolate poisoning" (p. 962).

Welch (1939), of the U.S. FDA, expanded the evaluation of the toxic action of potential preservatives, including Thimerosal, in mammalian tissue culture experiments. Welch (1939), when comparing the relative toxicity of Thimerosal with other germicide compounds such as phenol or iodine, determined that Thimerosal was, by several orders of magnitude, the most toxic compound tested.

In addition, Welch and Hunter (1940), again of the U.S. FDA, continued their previous research by reporting on the toxicity indices of germicides with human and guinea pig blood. The researchers determined the toxicity indexes for each germicide tested, by comparing the highest dilution producing inhibition in human cells or in guinea pig cells with the highest dilution that was bactericidal for staphylococci. Their experiments showed that Thimerosal was, in fact, considerably more toxic for human cells than bacterial cells (toxicity index = 5.7). Furthermore, it was observed, among the 10 germicides tested, that Thimerosal had the ninth worst toxicity index. With regard to Thimerosal, the researchers concluded, "It becomes obvious then that if any antiseptic destroys the function of the leukocyte much more readily than it kills bacteria there is little hope that it act efficiently as a chemotherapeutic agent" (p. 136).

Kinsella (1941) described a cases series of 13 patients with bacterial endocarditis that received Thimerosal treatment. It was observed that all patients receiving the Thimerosal treatment died, and that following autopsy, some of the patients were determined to have died of mercury poisoning from the Thimerosal treatment. For example, one report recorded, "Female, aged 23. Onset: Sore

throat treated with sulfanilamide. Later fever and pain the left chest. Examination: Systolic murmur second i.c.s left. Blood cultures: Non-hemolytic strep. 37 times 50 colonies per c.c. Clinical Diagnosis: Subacute bacterial endocarditis pulmonic valve (congenital). Treatment: Merthiolate. Autopsy: Healing pulmonary endarteritis—mercury poisoning" (p. 985). In light of determination that the treatment with Thimerosal produced mercury poisoning in humans, the suggestion was made to significantly limit Thimerosal exposure in humans due to its toxicity and potential hazards.

Despite the aforementioned concerns, however, large amounts of Thimerosal were purchased by the United States Government, for use in the war effort, from 1941 to 1945. During this time, the U.S. Army scrutinized the use of Thimerosal as a preservative in blood products. On 20 February 1941, the National Institutes of Health issued minimum requirements for normal human plasma, indicating that a sufficient amount of a suitable preservative should be added to the product (Kendrick, 1989).

In the first of several meetings of the Subcommittee on Blood Substitutes of the U.S. Army, it was noted that the Blood Transfusion Association of New York found Thimerosal unsatisfactory as a preservative (Kendrick, 1989). Specifically, it considered the instance from 1940 in which a large percentage of liquid plasma containing 1:10,000 Thimerosal, which had been collected in New York City, arrived in Britain, contaminated with viable organisms (Kendrick, 1989). At that time, a publication that questioned Thimerosal as a "preservative" concluded:

> In a recent study of protein sulfhydryl groups Hellerman, Chinard and Deitz point out that organometallic compounds of the type R-Hg-X . . . form poorly dissociated protein mercaptides by combination of the organic mercurial with proteins and thiol groups. According to Fildes the formation of such mercaptides is the basis for the bacteriostatic action of mercury. Such sulfhydryl groups are present, however, not only in bacteria but in plasma and other proteins. Bacteriostatic action of such organomercuric compounds in the presence of serum is therefore largely prevented by competition of reactive groups on the serum proteins for the mercury. This presumably is the basis of the finding that the 'activity of a mercurial antiseptic in serum is reduced to 0.33–0.0007 percent of its activity in saline.' Ignoring these chemical facts can be responsible for very serious occurrences, such as the arrival in England of plasma 'preserved' with 1:10,000 Merthiolate containing viable microorganisms . . . In our experience 1:10,000 Merthiolate has not been able to insure the sterility of stored liquid plasma. The contaminations reported in this paper in plasma-saline mixture containing 1:10,000 Merthiolate are sufficient to be an argument against its use. The material found to be contaminated when tested after its arrival in England is further evidence that 1:10,000 Merthiolate cannot be considered the ideal preservative. (p. 1253)

Weighing these concerns, some of the subcommittee members argued that plasma was best stored without any preservative at all; however, a recommendation to this effect was waived when the subcommittee realized that commercial firms were not inclined to process plasma without a preservative. Then, at the 3 November 1941 meeting of the subcommittee, Veldee reported on a review of the literature, which had been delegated to Weiss and himself. He informed the subcommittee that Thimerosal apparently had some bacteriostatic value and possibly some bactericidal value. Nonetheless, Weiss was not willing to accept Thimerosal as a preservative unless a maximum limit was set on the dosage of plasma due to toxicity concerns. He also stipulated that the symptoms of mercurial poisoning must be published on the label of the can. The Fifth Revision of Minimum Requirements for Liquid or Dried Plasma, 8 January 1945, stated, "There is no preservative bactericidal to all probable contaminants in concentrations not dangerously toxic in the maximum human dose." Subsequently, the Sixth through Ninth Revisions (15 April 1949 through 15 May 1952) prohibited use of a preservative (Gibson, 1976; Kenrick, 1989).

Concurrently, Ellis (1943) published an article on the possible danger of using Thimerosal in ophthalmic ointments. In his report evaluating this use of Thimerosal, Ellis (1943) observed, "Merthiolate is capable of causing an inflammation of the mucous membrane in patients," (p. 266) and made a very strong recommendation, based upon his clinical experience and that of several other physicians, considering the adverse effects of Thimerosal use. He disputed the acceptance of Thimerosal in medicine. Referencing the potential ability of Thimerosal to produce permanent

damage in the patient during clinical use, Ellis proposed, "it may be advisable to withdraw this product from the market" (p. 266). It is important to note that this recommendation was made more than 6 decades ago, after Thimerosal had been on the market for only approximately 10 years.

Ellis (1947) continued his work on Thimerosal, and subsequently reported on an even larger case series of patients experiencing adverse reactions following application of Thimerosal. Based upon his further clinical experiences, as well as those of his medical colleagues, Ellis (1947) once again strongly rebuked those advocating the continued use of Thimerosal in clinical medicine, stating, "it may be dangerous to inject a serum containing Merthiolate into a patient" (p. 213).

Subsequently, Cogswell and Shown (1948) reported, "We have had recently the occasion to observe a patient with a severe reaction to tincture of Merthiolate . . . which manifested a local and general reaction" (p. 42). The authors also stated, "The patient was warned never again to use Merthiolate solutions" (p. 43). Placing the experience of this patient in a larger perspective, the authors stated, "Many severe reactions have been reported following the use of mercurial ointments and a lesser number due to antiseptics containing mercurials" (p. 42). Cogswell and Shown (1948) even dared to condemn their colleagues for their myopia in wrongly evaluating the therapeutic effects of Thimerosal in the clinical setting:

> When a reaction does result, it is important that it be recognized and the application of the drug ceased. Many of the reported cases are similar in that in spite of a reaction to Merthiolate, its use was being continued as a means of therapy to alleviate the result of the application. Hollander reported on a nurse who had severe dermatitis venenata for over two years due to continuous self medication with tincture of Merthiolate. Improvement was noted on discontinuing its use . . . reaction should be recognized to prevent further applications of the drug which would exacerbate or accentuate the illness. (p. 43)

Morton et al. (1948), under a grant from the Council on Pharmacy and Chemistry of the American Medical Association, published an article on the bacteriostatic and bactericidal actions of some mercurial compounds on hemolytic streptococci. They reported:

> The label on a bottle of 'Solution Merthiolate, 1:1,000, Stainless' purchased as recently as June 1947 states that it is 'a stable, stainless, organic mercury compound of high germicidal value, particular in serum and other protein media.' It is not highly germicidal and especially does not possess high germicidal value in the presence of serum and other protein mediums. The loss of antibacterial activity of mercurials in the presence of serum proves their incompatibility with serum . . . The comparative in vitro studies on mercurochrome, metaphen and Merthiolate on embryonic tissue cells and bacterial cells by Salle and Lazarus cannot be ignored. These investigators found that metaphen, Merthiolate and mercurochrome were 12, 35 and 262 times respectively more toxic for embryonic tissue cells than for Staphylococcus aureus. Nye and Welch also found the same three mercurial compounds more toxic for leukocytes than for bacterial cells. Not only is there direct toxic action of the mercurial compounds on the cellular and humoral components of the animal body, but there is also the possibility of sensitization. (p. 41)

Engley (1950) of the Biological Department, Chemical Corps, Camp Detrick, published an evaluation of mercurial compounds as antiseptics and judged mercurials to be inadequate as antiseptics:

> Mercurial compounds have not enjoyed a peaceful career as antibacterial chemicals since their popularization as germicides over sixty years ago (Kock, 1891) . . . During the ensuing years, other workers, using various techniques, have also shown that the antibacterial activity of mercurials is only slowly bactericidal and mainly bacteriostatic. This bacteriostasis is even nullified by the presence of many types of sulfur-containing compounds, including sulfides (Geppert, 1889), (Hunt, 1937), thioglycollate (Marshall, Gunnison, and Luxen, 1941), body fluids such as plasma (Johnson and Meleney, 1942), and other organic matter (Green and Birkeland, 1944). (p. 197)

Furthermore, and of even greater concern, was Engley's conclusion that mercurials, such as Thimerosal, "are ineffective *in vivo* and may be more toxic for tissue cells than bacterial cells, as shown in

mice (Nungester and Kempf, 1942) (Saber, 1942) (Spaulding and Bondi, 1947), tissue culture (Salle and Catlin, 1947), and embryonic eggs (Witlin, 1942) (Green and Birkeland, 1944), and with leucocytes (Welch and Hunter, 1940)" (p. 197).

Davisson et al. (1956) from the Lilly Research Laboratories reported on a molecular mechanism for Thimerosal induced cellular toxicity. Specifically, they described that the cellular toxicity of Thimerosal was the result of "partial ionization of the compound to go give a low but effective level of ethyl mercuri ion ($C_2H_5Hg^+$), which blocks enzymatic processes by combining with sulfhydryl groups on the enzymes" (p. 8).

Subsequently, Engley (1956) presented a paper to the 42nd midyear meeting of the Chemical Specialties Manufacturer's Association in Chicago. Engley overtly questioned the acceptance of Thimerosal as a preservative in vaccines and other pharmaceuticals products by stating:

> The use of mercurials as preservatives in vaccines and antisera is of considerable interest. These chemicals are added to protect against the introduction of organisms in multi-use containers in particular. We have always wondered about their efficacy in that both vaccines and antisera contain reactive groups to tie up these compounds. In a series of continuing experiments over the past several years we have begun to evaluate various preservatives in serum and vaccines under conditions of use. Employing stock vaccines and serum with and without preservatives and stored at varying lengths of time a contaminating dose of representative sporeformer (*Bacillus subtilis*) in the spore stage gram negative rod (*E. coli*) and gram positive coccus (*S. aureus*) were added. While the mercurial preservatives had good activity on initial addition, after storage of three, six or more months decreasingly less to negligible residual activity appeared to be left, indicating that the chemical was tied up by the protein of the biological or otherwise inactivated. A check on a series of over one thousand bottles of various biologicals from clinics obtained after use revealed that up to five percent contained micro-organisms. This would suggest that once these biologicals are in the hands of users a problem still exists. Regarding preservatives, one of the real problems existing in hospitals and clinics is the need for good preservatives in the routine eye dilators and nasal preparations of the decongestant type. Routine checks of these indicate a high percentage of contaminated solutions. In one instance we had direct evidence of upper respiratory cross-infection from the use of a common nasal dropper preparation in a clinic. (p. 205, 223)

Engley (1956) then gave an evaluation of the relative toxicity of mercurials, such as Thimerosal, by stating:

> The toxicity of chemicals used as drugs on or in the body has been of considerable interest since man first began exposing himself to various chemicals many years ago. Unfortunately there have not been good techniques for toxicity determinations of certain types of chemicals which might be really indicative of toxicity for humans . . . Graph 15 compares mercurial compounds and shows how they fit in with other compounds in toxicity . . . Mercurochrome appears to be the least toxic ranging down through Merthiolate . . . One point should be made here. Bichloride of mercury has always been pointed out as an extremely toxic mercurial and the organic mercurials were supposed to be much less toxic but according to these data we find bichloride right in the middle of the organic mercurials in regard to cell toxicity . . . mercurial antiseptics proved to be more toxic than the antibiotics in common usage. (p. 223–225)

Finally, it should be noted, with respect to the toxicity experiments undertaken by Engley (1956), that he determined Thimerosal was significantly toxic to human tissue culture cells at a concentration of 10 ppb.

PLANT AND ANIMAL MODELS OF ETHYLMERCURY TOXICITY

Interestingly, prior to studies conducted on the toxicity of ethylmercury in animals, a series of studies was conducted to evaluate its toxicity to plants. Sass (1937) reported on the histological and cytological pathology induced by ethylmercury poisoning in corn seedlings. Sass (1937) described, "The use of dusts in which the active ingredient is ethyl mercury . . . produces a characteristic

malformation of the seedlings of corn and other cereals" (p. 95). He subsequently went onto describe based upon his series of experiments:

> In corn seedlings grown from nontreated seed, the leaf primordial and apical meristem of the coleoptile have the structure characteristic of meristematic tissues. The cells are small, polygonal, compactly arranged, and of uniform size. These cells are strictly uninucleate . . . Seedlings from treated seeds exhibit varying degrees of distortion of cells, tissues and organs in proportion to the severity of the gross external symptoms . . . The formation of new cells and new leaf primordial cases, the existing cells continuing their excessive irregular enlargement . . . The cells of the hypertrophied tissues of corn seedlings were found to be multinucleate. The number of nuclei in a cell varies from one to more than 10 . . . The 'giant nuclei' are clearly polyploid. (p. 95)

One of the earliest studies to evaluate the effects of ethylmercury on animals was published in 1950 (Trakhtenberg, 1950). In this study, the toxicity of the ethylmercury compounds was examined in mice. White mice were exposed to ethylmercury compound vapor, and the animals were subsequently observed for clinical signs of toxicity and mortality. Those studies found:

> Acute exposure to the organic mercury compounds caused symptoms indicative of serious respiratory and nervous system disruption: labored respiration, cyanosis of the nose, tail and ears, and hind limb paralysis. All animals died 6 to 15 hours after exposure . . . In the chronic study, the central nervous system was the main site of involvement. Mice exposed to the organic compounds showed a hind limb paralysis that gradually spread to the front limbs. Death occurred by day 38. (p. 13–17)

Subsequently, researchers reported additional outcomes for an ethylmercury compound in animals (Oliver & Platonow, 1960). These researchers reported that ethylmercury exposure, "produced signs of central nervous system or gastrointestinal disturbance, or both in cattle . . . It caused progressive degenerative changes in the heart . . . It produced diffuse lesions in the cord, cerebellum, and cerebrum and caused glomerulonephritis" (p. 914–915).

The effects of ethylmercury poisoning were also observed in mass poisonings of swine on several farms (Birbin et al., 1968). It was noted:

> On the October' Collective Farm in Tatishchevo District, 383 of 414 swine of various ages were affected during August (1967), the acute period; 121 died and 145 in the agonal state had to be slaughtered. By November, another 44 animals had died. On the Fedorov' State Farm in Marx District, 211 of 444 swine were affected . . . The first signs of poisoning appeared in suckling pigs and fatling gilts 20 to 25 d after beginning feeding on the treated grain; in sows, the signs appeared in 30 to 40 d. At first, the animals refused food and water and became restless. There was some nasal mucous secretion. Then weakness in the hind limbs appeared, with different types of movement coordination disorder. Some animals showed spinal involvement. Signs of neural disorders were quite clear, including muscular tremors, convulsional jerking of the extremities and titanic contractions of the pelvic musculature. As the conditions worsened, the animals lay on their stomachs or sides, developing varying degrees of paralysis with loss of pain sensation, rapid breathing, etc. The younger swine almost all died within 3 to 6 d after the symptoms started; the sows' condition persisted longer until death (6 to 11 d) and 40 to 45% of the affected animals died. In some instances, the swine suffered the above symptoms, including partial or complete loss of vision, for 2 to 3 months. The autopsy findings were initially the same in all the animals, the most constant changes being noted in the intestines. The intestinal mucous membrane was covered with dryish, dirty yellow or brownish-green deposits connected to the underlying tissue . . . The fact of a delay in the appearance of symptoms following Granosan must be taken into account in diagnosing organomercury poisonings. The clinical symptoms and pathological-anatomical changes in mass poisonings of swine with Granosan to a great extent recall the course of infectious diseases . . . so that mercury poisoning should be eliminated during a differential diagnosis. (Birbin et al., 1968, p. 60–61)

Additionally, heavy losses were reported to have occurred in a poultry-yard due to feed treated with ethylmercury (Tishkov et al., 1968). The clinical symptoms observed in chickens on the last

day before death were depression, spasm, paralysis of the limbs, swollen heads, and elevated temperature. It was observed that mercury residues were detectable in the kidneys, liver, muscles, skin, brains, lungs, hearts, ovaries, and eggs, and depending on the duration and intensity of the exposure, mercury residues could be detected in the chicken tissues for as long as 120 d after the poisoning.

Oharazawa (1968) published a study examining the ability of ethylmercury exposure during pregnancy to induce fetal damage in mice. He observed that injection of ethylmercury during pregnancy significantly reduced the weights of developing fetuses in utero and produced significant increases in fetal malformations and the incidence of unstable chromosomes characterized as polyploidy, chromatid gaps, or fragmented, in comparison to unexposed controls.

By 1971, researchers had become more sophisticated, evaluating the effects of ethylmercury on several successive generations of offspring. Goncharuk (1971) administered an ethylmercury compound to albino rats, and subsequently, these animals were mated. Investigations were made of the sexual cycle, and the viability, physical development, and fertility of the progeny of the first and second generations. It was observed that females that had been previously exposed to the ethylmercury compound became pregnant only on the fourth or fifth occasion when they were placed with males when in estrus, whereas nonexposed control females became impregnated on the first or second mating. The number of offspring per litter was significantly smaller in the animals treated with the ethylmercury compound than in controls. It was also observed that young rats from mothers that had been previously exposed to the ethylmercury compound died significantly more frequently than controls. Observations of the first-generation progeny revealed a lag in weight growth in comparison to controls, especially during the first and second months of extrauterine life. In addition, the first-generation progeny had birth weights that exceeded those of the control group, and studies of skeletal ossification in the young rats revealed a large number of cases with retardation of the appearance and development of ossification centers in bones of the fore and hind paws. Studies of the organs and tissues of the first generation progeny revealed mercury in the stomach and intestine at birth and in the first week of life, apparently on account of the entry of mercury through the placental barrier and by way of their mother's milk. Subsequently, it was noted that the first-generation progeny of mothers that had been previously exposed to the ethylmercury compound had significantly reduced fertility in comparison to controls. The second generation progeny had low viability, lagged in their weight growth, and were retarded with respect to ossification in several cases. Finally, it was then observed when mating the second generation progeny that there was a significant decrease in fertility in comparison to the control group.

A later study on pheasants by the Bureau of Sport Fisheries and Wildlife, Patuxent Wildlife Research Center, concluded that ethylmercury compound exposure at a level equivalent to 12.5 ppm mercury was lethal to adult animals and at 4.2 ppm mercury impaired reproduction in the species (Spann et al., 1972). These researchers also reported:

> Ethyl mercury p-toluene sulfonanilide (active ingredient of Ceresan M) at a dietary concentration of 30 parts per million (12.5 parts of mercury per million) was lethal to adult ring-necked pheasants. Egg production and survival of third-week embryos were sharply reduced when breeders were maintained on feed containing 10 parts of this compound per million (4.2 parts of mercury per million) . . . Since similar residues of mercury have been found in eggs of wild pheasants and several species of aquatic birds, we conclude that mercury pollution may be sufficiently high in some areas to affect avian reproduction. (p. 328, 330)

Mukai (1972), with a grant from the U.S. National Institutes of Health, reported on an animal model of ethylmercury-cysteine-induced encephalopathy using mice. Mukai (1972) observed:

> Mice injected intraperitoneally with EMC (Ethyl Mercuri-S-Cysteine) labeled with tritium showed the typical neurologic symptoms of mercury poisoning. Administration of EMC in a concentration of 0.3 mg/0.5 mL saline per day for at least eight days was a prerequisite for significant accretion of EMC in the central nervous system. The extent and distribution of cell damage were highly predictable,

> and selective necrosis of the small granular neurons in the koniocrotex, and neostriatum was a constant finding. Autoradiographic study has suggested that the astroglial cell compartment plays a role in conveying the mercury complex into neurons. (p. 102)

Subsequent research by Tryphonas and Nielsen (1973), which was sponsored by the Medical Research Council of Canada, not only showed that ethylmercury produced a consistent and predictable pattern of encephalopathy, but also that it induced severe developmental toxicity at very low doses. It was described:

> Ethylmercuric chloride (EMC) w(as) used to produce chronic alkylmercurial poisoning in young pigs. A dosage of 0.19 to 0.76 mg. of Hg/kg. of body weight per day was used . . . The resulting toxicosis was primarily related to the nervous system, in which neuronal necrosis followed by secondary gliosis, capillary endothelial proliferation, and additional neuronal necrosis due to developing degenerative arteriopathy in the blood vessels supplying injured gray matter were seen. In other systems, degeneration of hepatocytes and renal tubular cells were commonly occurring lesions in pigs . . . edema of the mescolon, necrosis of the epithelium, and degenerative arteriopathy in the submucosa were seen most consistently in the esophagus and large intestine of pigs . . . The results proved that . . . EMC, if fed at low concentrations . . . were highly poisonous . . . Finally, since the alkylmercurial moiety is absorbed and stored as such for considerable lengths of time in . . . cells, the public health implications . . . cannot be overlooked. (p. 379, 391)

Furthermore, Wright et al. (1973) from the U.S. Department of Agriculture evaluated the toxicokinetics of mercury in the tissues of cattle and sheep administered ethylmercury. These researchers showed that significant levels of mercury were detectable in multiple organs including the blood, kidney, liver, and muscle for significant lengths of time following exposure to ethylmercury. Additionally, these researchers found that mercury crossed the blood-brain barrier, and resulted in significant levels of mercury in the brain for more than 20 wk (>140 d) following administration of the last dose of this ethlymercury compound. In another study that examined swine administered ethylmercury, it was found that significant levels of mercury were detectable for more than 8 mo (>240 d) following administration of the last dose of the ethylmercury (Saley, 1970).

Yonaha et al. (1975), from the National Institute of Hygienic Sciences, also evaluated the uptake, retention, and toxicity of ethylmercury in several organs, when administered to mice. These researchers reported:

> Ethylmercury chloride was highly incorporated into the brain . . . It may be presumed that manifestations of symptoms after exposure of organic mercury compounds is not merely related to mercury levels and not always in need of organic forms in the brain . . . The clinical signs and pathological findings caused by methylmercury compounds in animal experiments were known to be similar to Minamata disease manifested in human. At the same time, the symptoms in cats, calves, and mice poisoned by ethylmercury compounds were similar to those in methylmercury compounds. Further, as reported by Sebe, et al., alkylmercury compounds having short carbon chains (C_1-C_3) bring about the specific neurotoxicity and the signs of poisoning in rats. (p. 1718)

ETHYLMERCURY POISONING IN HUMANS

Spanning the 1950s and 1960s, a series of population outbreaks of ethylmercury poisonings occurred in Iraq, following ingestion of Granosan M, an antifungal that was used to prevent plant root disease in grain products. Beginning in 1955, the Iraqi Ministry of Agriculture supplied farmers with seeds dusted with the fungicide. Farmers had been given frequent warnings against using the treated seed for food, and as a result, most of them were aware of the highly lethal effect of eating dusted seed. Out of ignorance or neglect, however, some unfortunate farmers and their families consumed the seed and became the victims of mercury poisoning. Consequently, these farmers developed a number of serious mercury-related conditions (Jalili & Abbasi, 1961; Al-Kassab & Saigh, 1962; Dahhan & Orfaly, 1962; Damlugi, 1962). Specifically, it was reported:

> Poisoning by a fungicide used for seed-borne diseases of cereals, ethyl mercury p-toluene sulfonanilide (Granoson M, Dupont) is described. It affected a large number of farmers and their families who used the dressed seed in the preparation of home-made bread. Many systems were involved, including the kidneys, the gastrointestinal tract, the skin, the heart, and the muscles, but involvement of the nervous system was the most constant with disturbance of speech, cerebellar ataxia, and spasticity. Mental abnormalities were occasionally observed . . . In 1956 many cases of mercury poisoning were observed in the North of Iraq, and more than 100 cases were admitted to Mosul Hospital with 14 deaths. In 1960, many farmers from the central part of Iraq were affected and 221 patients were admitted to one hospital in Baghdad. Other patients went to other hospitals. (Jalili & Abbasi, 1961, p. 303)

Later, a significant series of patients in Russia was observed to suffer from serious toxic outcomes following ingestion of ethylmercury and occupational exposure to ethylmercury (Shustov & Syganova, 1970; Nizov & Shestakov, 1971). Early signs of exposure included general weakness, pains, tachycardia, and headache. Thereafter, it was observed that appetite decreased until, at last, food was refused; there was also nausea, liquid stool, disordered sleep, decreased memory, and pain in the extremities. Most of the patients recovered, but death was observed following exposure in some of the patients. Such case studies clearly demonstrate the severe toxicity of this compound to humans and document its effect on multiple systems of the human body due to acute exposure.

Not only acute exposure, however, but also low-dose exposure has produced significant impairment in human beings, a fact documented by Mukhtarova (1977). Mukhtarova (1977) examined the late after-effects upon the nervous system following chronic low-dose exposure to ethylmercury. The researcher reported:

> A total of 25 persons exposed to multiple effects of low ethyl-mercuric-chloride concentrations were subjected to a clinical examination in dynamics 1 ½ and 3 years after exposure to the compound. In investigations clinico-physiological (EEG, Asschner-Dagnini reflexes, etc) and biochemical (catecholamines, sugar, mercury, DDT, DDE in the urine, etc) methods were employed. The pathology of the nervous system presented certain peculiarities by comparison with early period. In evidence were changes in the simpatico-adrenal system function, vascular lesions of the brain after the type of transient derangements of the cerebral circulation in the vertebro-basilar basin and angiospasms, diffuse changes in the nervous system with predominant involvement of the hypothalamic cerebral structures and in some cases psychiatric disturbances were on record. (p. 4–7)

Over time, further incidents of mercury poisonings by ethylmercury compounds continued to offer substantial evidence and disclose a pattern of extreme toxicity produced by ethylmercury in humans. For example, Cinca et al. (1980) reported on accidental ethylmercury poisoning with nervous system, skeletal muscle, and myocardium injury and stated, "Four case reports are presented of patients who ate the meat of a hog inadvertently fed seed treated with fungicides containing ethyl mercury chloride. The clinical, electrophysiological, and toxicological, and in two of the patients the pathological data, showed that this organic mercury compound has a very high toxicity not only for the brain, but also for the spinal motor neurons, peripheral nerves, skeletal muscles, and myocardium" (p. 143).

As another example, Zhang (1984) evaluated clinical symptoms observed in patients with ethylmercury chloride poisoning and reported, "Forty-one patients in the Peoples Republic of China were poisoned by ethyl mercury chloride, caused by the ingestion of rice that had been treated with the chemical. A dose-response relationship was found. Five months after the onset of the intoxication, the patients were still in poor condition" (p. 251).

Derban (1974) even reported on clinical symptoms observed in children following ethylmercury poisoning of 144 people in a rural Ghana village, "Four children developed disturbance of speech which led to stammering and scanning. Mental abnormality was observed in one boy who showed occasional outburst of anger unrelated to circumstances. A girl developed encephalitis and became completely paralyzed in both upper and lower limbs, with incontinence of urine and feces and complete loss of speech" (p. 50).

Paramount in the historical scientific record of exposures to ethylmercury compounds are the first reports of human fetal poisonings. Bakulina (1968) described in a study on a human fetal poisoning:

> Granosan (ethylmercury chloride) is capable of passing through the placental barrier and penetrating into the fetus, causing in the organs of the latter grave pathological changes. The permeability of the placental barrier for organic mercury compounds finds its confirmation in the presence of mercury in the placenta and organs of the fetus . . . Breast feeding was found to be conducive to accumulation of mercury in the organism of newborns, since the mothers' milk, as a rule, disclosed the presence of this element. A very important point was that fetal intoxication was possible for as long as 3–4 years after the mother poisoned. (p. 63)

By the early 1970s, researchers developed an overall clinical picture of ethylmercury poisoning in fetuses following large-scale ethylmercury poisoning episodes (Mal'tsev, 1972; Ramanauskayte & Baublis 1973).

Ramanauskayte and Baublis (1973) stated that, after exposure to ethylmercury-treated seeds:

> Intrauterine poisoning in infants was observed(.) . . . (C)hildren on the whole are more susceptible to mercury than adults(.) . . . Serious functional disorders of the central nervous system, hydrocephalus, cerebral paralysis, and spasms were observed in infants. Toxic encephalomyeloradiculoneuritis with prevalence of the syndromes of lesions of the cerebral cortex, brain stem, cerebellum, myelitis, peripheral neurites, lesions of the motor centers, of the pyramidal tracts, and encephalitis with irregular alpha-rhythm were observed . . . Epilepsy lasting up to 2 years was observed in 10% of all cases. Prevalence of vegetoneurotic syndromes, tachycardia, bradycardia, arrhythmia, acrocyanosis, liability of the arterial pressure, and reduction of the blood cholinesterase activity were found in older children with chronic poisoning. The lesions of the liver, kidney, heart and gastrointestinal tract were much less pronounced than those of the central nervous system. Sodium thiosulfate, glutamic acid, vitamin B and C complexes, glucose, and diuresis are essential for detoxification. (Ramanauskayte & Baublis, 1973, p. 56–60)

Confirming the tremendous danger of ethylmercury compounds to children, Mal'tsev (1972) reported that in cases of children poisoned with ethylmercury, the onset of symptoms usually occurred many weeks following exposure. The first symptoms of ethylmercury poisoning in children included asthenia, fatigability, and loss of appetite, followed by nausea, vomiting, liquid feces, abdominal pains, and elevated temperature. Subsequently, the neurological syndrome developed and consisted of symptoms such as ataxia, dysarthria, psychomotor disturbances, and sleep disturbances. The researcher reported that damage to the nervous system may be irreversible even following low-dose exposure. Mal'tsev (1972) also commented that, upon autopsy of children who died of ethylmercury exposure, degenerative, inflammatory, and necrotic alterations were seen, as well as hemorrhages in the central nervous system, kidney, liver, heart, and intestines. Mal'tsev (1972) also reported that ethylmercury appeared to be the most dangerous to the embryos during the third and four months of pregnancy.

EMERGING EVIDENCE OF THE TOXICITY OF THIMEROSAL

More recent scientific examination and case studies have shown that Thimerosal is not only toxic but also lethal at comparable levels, in humans and animals.

Nelson and Gottshall (1967) from the Division of Biologic Products, Bureaus of Laboratories, Michigan Department of Public Health, published, "Pertussis vaccines preserved with 0.01% Merthiolate are more toxic for mice than unpreserved vaccines prepared from the same parent concentrate and containing the same number of organisms . . . An increase in mortality was observed when Merthiolate was injected separately, before or after an unpreserved saline suspension of pertussis vaccine" (p. 590).

From 17–19 June 1971, an international conference and its associated advisory committee reviewed the environmental toxicity from mercurials (Suzuki et al., 1973). One of the key areas

examined at this conference was the metabolic fate of ethylmercury salts, with a specific emphasis on Thimerosal, in humans. That committee reported:

> The toxic nature of ethylmercury has been considered to be fairly similar to that of methylmercury salts. In the recommendations of the international committee on Maximum Allowable Concentration for mercury and its compounds, ethylmercury was grouped with methylmercury. Reports on human intoxication with ethylmercury salts have usually reported symptoms similar to those of methylmercury, which is accentuated by the typical neurological symptoms, although there have been a few reports that noted slightly different symptoms from the typical features of methylmercury poisoning. In acute experiments on animals, ethylmercury has an LD_{50} similar to that of methylmercury salts and a high neurotoxicity similar to that of methylmercury. (p. 209–210)

In addition, the report stated:

> By using methods for estimating the inorganic and total mercury content of biological specimens, the metabolism of ethylmercury salts was studied in man and animals. The [carbon–mercury bond] C–Hg of ethylmercury salts was able to break fairly rapidly and to a great extent in men, who were patients and were transfused with a commercial product of human plasma containing 0.01% (Thimerosal) sodium ethylmercurithiosalicylate, and also in mice injected subcutaneously or intravenously with ethylmercurithiosalicylate solution. The increasing level of inorganic mercury and its percentage to total mercury content in the brain were quite distinguishable with post-injection time in mice, which resulted in longer biological half-time of total mercury than that reported for methylmercury injection. (p. 209)

Itoi and his colleagues (1972) conducted a series of experiments to evaluate the reproductive toxicity of Thimerosal in rabbits. They observed that injection of increasing doses of Thimerosal (from 0.02 to 0.2% solutions) into pregnant rabbits resulted in significantly increased numbers of dead fetuses (up to 18% of fetuses died following exposure) and increased fetal congenital anomalies (up to 9.1% of fetuses developed congenital anomalies following exposure) in comparison to rabbits injected with physiological saline.

Axton (1972) also reported on a series of 6 patients (4 children and 2 adults), 5 of whom died following injection with chloramphenicol preserved with abnormally high levels of Thimerosal. He reported that there was something wrong with the chloramphenicol injections. This problem was first suspected on 23 October 1969, following the appearance of skin necrosis over the injection sites in 4 children, and the drug was withdrawn from the pediatric wards. Preliminary investigation of the vials used, for pH, concentration of chloramphenicol, and bacteriology, revealed no abnormality. Heavy metal contamination was not considered at this stage.

Case 1 was the first to die (6 November 1969), and on the morning of his death, the combination of albuminuria and glycosuria with mental symptoms suggested poisoning, possibly by a heavy metal. The suspicion was supported by the necropsy findings later in the day (large swollen kidneys). Reference was again made to the local manufacturers of the chloramphenicol, and it was discovered that 0.51 kg of Thimerosal was used in the preparation of one thousand 1-g vials of chloramphenicol. The correct amount should have been 0.51 g. The amount of Thimerosal in each vial was 1000 times too much.

The FDA undertook a comprehensive review of the safety and effectiveness of over-the-counter (OTC) medicines in 1974. As one facet of this review, a panel of experts was assembled to review the safety and efficacy of OTC drugs containing mercury. The Advisory Review Panel on OTC Miscellaneous External Drug Products began its slow-paced review in 1975.

Independently of the FDA's review, Gasset et al. (1975), under a grant from the US National Institutes of Health, examined mercury distribution following administration of Thimerosal to animals. They stated, "A comparison of topical and subcutaneous administration of Thimerosal to rabbits shows that a substantial concentration of mercury was present in blood and tissues of the treated animals and their offspring. Thimerosal was found to cross the blood-brain and placenta barriers" (p. 52). These researchers also determined that administration of Thimerosal caused a dose-dependent significant increase in fetal mortality.

Blair et al. (1975) also examined mercury distribution and form following administration of Thimerosal to animals. In 1975, the authors reported that squirrel monkeys were dosed intranasally with saline or Thiomersal (sodium ethylmercurithiosalicylate, 0.002% w/v) daily for 6 mo. The total amounts of Thiomersal given during the 6 month period were 418 μg (low-dose group) and 2280 μg (high-dose group). This was equivalent to 207 μg mercury and 1125 μg mercury. The dose differential was achieved by more frequent administration to the high-dose group. Mercury concentrations were significantly raised over control values in brain, liver, muscle, and kidneys, but not blood. Concentrations were highest in kidneys, moderate in liver and lowest in brain and muscle. Much of the mercury was present in the inorganic form (37–91%). The authors concluded that "accumulation of mercury from chronic use of thiomersal-preserved medicines is viewed as a potential health hazard for man" (p. 171).

The U.S. Veterans Administration and the U.S. National Institutes of Health funded research published by Van Horn et al. (1977) that examined the toxic effects of Thimerosal on human tissue culture cells. These authors commented:

> Widespread use of the mercurial-containing preservative Thimerosal as an antibacterial agent in ophthalmic drugs and solutions warranted an investigation into its possible cytotoxic effects on the functional and ultrastructural integrity of the corneal endothelium. . .(scanning electron microscopy) SEM and (transmission electron microscopy) TEM of the endothelium of corneas perfused with 0.0005 percent Thimerosal for 5 hours revealed condensed mitochondria, cytoplasmic vacuoles, and cytoplasmic flaps at the apical end of the cellular junctions. Perfusion of higher concentrations (0.001 and 0.005 percent) of Thimerosal in (glutathione bicarbonate Ringer's solution) GBR resulted in increases in corneal thickness after 2 hours and irreversible ultrastructural damage to the endothelial cells by 5 hours. Corneas perfused with 0.01 and 0.1 percent Thimerosal in GBR showed a rapid and immediate increase in corneal thickness and endothelial cell death and necrosis within 1 hour. It is postulated that the mercury in Thimerosal becomes bound to the cell membrane protein sulfhydryl groups, causing an increase in cellular permeability. These results suggest that the prolonged exposure of the corneal endothelium to Thimerosal in the accepted antimicrobial dosage of 0.005 to 0.001 percent may result in functional and structural damage to the endothelium . . . It is therefore concluded that ophthalmic solutions containing Thimerosal should not be used. (p. 273–274, 280)

Parry (1977) utilized yeast cultures for the detection of environmental mutagens using a fluctuation test. He described:

> A microbial fluctuation test, modified for the detection of environmental mutagens has been evaluated using a number of strains of the yeast *Saccharomyces cerevisiae*. Auoxtrophic diploid cultures of yeast which produce prototrophic colonies by both mitotic gene conversion and mutation have been extensively utilized for the detection and evaluation of chemicals showing genetic activity. A number of the yeast strains utilized were shown to be suitable for use in the fluctuation test . . . The yeast strains respond to doses of mutagens at least a 100-fold lower than that required in a conventional short exposure treat and plate experiment. In experiments involving the induction of mitotic gene conversion at the tryptophan-5 and histidine-4 loci in the flucuation test significant increases in prototrophic cells were produced in the presence of . . . the preservative Thiomersal (0.0001 μg/mL) . . . The results demonstrate that the fluctuation test provides an extremely sensitive assay for the detection of chemicals which show genetic activity in yeast at non-toxic concentrations. (p. 165)

It should be noted that Parry (1977) observed Thimerosal induced significant genetic alterations in yeast cells at a level <1 ppb.

Fagan et al. (1977) published a case series of children who were apparently poisoned by Thimerosal. Fagan et al. (1977) reported, in a study funded by the National Institute of Environmental Health Sciences of the U.S. National Institutes of Health, that between 1969 and 1975, 13 cases of exomphalos were treated by Thimerosal. The authors analyzed the mercury content in tissues from 10 of the patients who had died. Upon reviewing the test results, the researchers stated:

> The results showed that Thiomersal can induce blood and organ levels of organic mercury which are well in excess of the minimum toxic levels in adults and fetuses . . . Although Thiomersal is an ethyl mercury compound, it has similar toxicological properties to methyl mercury and the long-term neurological sequelae produced by the ingestion of either methyl or ethyl mercury-based fungicides are indistinguishable. (p. 962–963)

The authors also emphasized, "the fact that mercury readily penetrates intact membranes and is highly toxic seems to have been forgotten. Equally effective and far less toxic broad-spectrum antifungal and antibacterial . . . antiseptics are currently available" (p. 964).

Also published in 1977 were the results of a large-scale prospective human epidemiological study (the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke, the U.S. Public Health Service, and the U.S. FDA) on drug exposures during pregnancy and their association with birth defects (Heinonen et al., 1977). This study reported:

> Between 1958 and 1965, under the auspices of the National Institute of Neurological and Communicative Disorders and Stroke, a prospective study of over 50,000 pregnancies was undertaken with the main objective of determining whether there are factors during pregnancy or delivery that are related to the risk of cerebral palsy or other neurological outcomes. This study ultimately became known as the Collaborative Perinatal Project. Among many items of data obtained, drug use was recorded during pregnancy, and birth defects identified in the children were recorded subsequently. With the growing realization that drugs are sometimes teratogenic, it became mandatory to evaluate the data from the perspective . . . The purpose of this book is to present data on drugs used by 50,282 gravidae in relation to birth defects identified in children. (p. viii)

The conclusion of these researchers with regard to Thimerosal:

> The measure of association presented is a standardized relative risk (SRR) with its 95% confidence limits. The SRR is the ratio of the observed number to the expected number of malformed children. Since the SRR takes into account potential confounding variables, it represents the best estimate of the relationship between a drug and a malformation . . . Finally, thiomersal . . . was associated with malformations overall and with uniform malformations. (p. 299, 313)

Specifically, it was determined that Thimerosal exposure during the first 4 mo of pregnancy was associated with a statistically significant increased risk (SRR = 2.69) for birth defects.

Anundi et al. (1979) described a molecular mechanism by which Thimerosal exposure rapidly induced cellular oxidative stress and subsequent cellular lysis following glutathione depletion, and that the addition of cysteine could reverse the cellular toxicity of Thimerosal. Specifically, it was determined:

> Compounds are known which interact with lipids and proteins in such a way that both lipid peroxidation and protein alkylation have been considered a cause of toxicity . . . it has become evident that (glutathione) GSH protects against protein alkylation and that electrophilic compounds which deplete GSH may alkylate proteins. The main point in this communication is that cellular damage following GSH depletion may be explained by lipid peroxidation which destroys the cell before the alkylation of proteins, as a component of cellular damage, is expressed. (p. 45–46)

In 1980, the FDA's Advisory Review Panel on OTC Miscellaneous External Drug Products finally delivered its report to the FDA. It reviewed 18 products containing mercury and found them all either unsafe or ineffective for their stated purpose of killing bacteria to prevent infections. In terms of effectiveness, the panel stated, "mercury compounds as a class are of dubious value for antimicrobial use" (Subcommittee on Human Rights and Wellness, 2003, p. 61). They also stated, "Mercury inhibits the growth of bacteria, but does not act swiftly to kill them" (Subcommittee on Human Rights and Wellness, 2003, p. 61). In fact, the panel cited a study, conducted in 1935, on the effectiveness of Thimerosal in killing staphylococcus bacteria on chick heart tissue. The study

determined that Thimerosal was 35 times more toxic to the heart tissue it was meant to protect than to the bacteria it was meant to kill. In terms of safety, the panel cited a number of studies demonstrating the highly allergenic nature of Thimerosal and related organic mercury products. For example, it cited a Swedish study that showed that 10% of school children, 16% of military recruits, and 18% of twins, and 26% of medical students had hypersensitivity to Thimerosal. They stated that while organic mercury compounds, like Thimerosal, were initially developed to decrease the toxicity of the mercury ion, Thimerosal was actually found to be more toxic than bi-chloride of mercury for certain human cells (Subcommittee on Human Rights and Wellness, 2003, p. 61). By way of summary, "The Panel concludes that Thimerosal is not safe for OTC topical use because of its potential for cell damage if applied to broken skin, and its allergy potential. It is not effective as a topical antimicrobial because its bacteriostatic action can be reversed" (Subcommittee on Human Rights and Wellness, 2003, p. 61).

Despite the fact that the FDA expert committee found Thimerosal and other ethylmercury compounds to be unsafe and ineffective for OTC products in 1980, the process to remove mercurials from these products was excruciatingly slow. As a first step in the process, the agency published Advanced Notice of Proposed Rules or Notice of Proposed Rules, publicizing the recommendations of their Advisory Panel on OTC Miscellaneous External Drug Products to ban Thimerosal and other mercurial-containing products in 1980, 1982, 1990, 1991, 1994, and 1995. No action was taken on any of these occasions (Subcommittee on Human Rights and Wellness, 2003). Decisive action from the FDA on the issue of mercury in OTC products would not come until 1998, 18 years after its Advisory Panel first acknowledged Thimerosal's "lack of safety" in topical ointments (Subcommittee on Human Rights and Wellness, 2003).

COMMENTARY TO END THE MEDICINAL USE OF THIMEROSAL

Heyworth and Truelove (1979) undertook a study to evaluate the potential adverse effects of Thimerosal-containing immune globulin preparations. These researchers found, "Merthiolate contains an ethyl group directly joined to a mercury atom. Organic compounds containing an alkyl radical directly attached to a mercury atom are more toxic to human subjects than are other types of mercury compounds. Considerable accumulation of mercury occurs in tissues of mice injected with ethyl mercury compounds, and in 1 human subject receiving intravenous infusions of Merthiolate-containing plasma tissue accumulation of mercury was also observed" (p. 331). The researchers went onto conclude:

> For many years, Merthiolate has been known to have anti-microbial activity. When it was first introduced as an anti-microbial preservative, little information about the fundamental biological effects of organic mercury compounds was available. We should like to suggest that Merthiolate should now be regarded as an inappropriate preservative for anti-lymphocytic globulin preparations and other materials which are intended for administration to human subjects. (p. 333)

Matheson et al. (1980) published a case report of mercury-poisoning induced by long-term injection of Thimerosal-containing gamma globulin. They found that the patient developed pink, scaling, pruritic palms and soles, flushed cheeks, photophobia, irritability, a fine tremor, altered sensation in his fingertips, and slowed nerve conduction velocity. These authors reported, "Most commercially available gammaglobulin preparations contain Merthiolate (sodium ethylmercurithiosalicylate), a mercury-containing compound, which serves as a bacteriostatic agent. Thus, patients receiving regular injection of gammaglobulin are potentially at risk for the development of mercury toxicity. . . It would appear, therefore, that Merthiolate which is used as a preservative in a commercially available gammaglobulin preparation represents a potential hazard to patients" (p. 153, 155).

Forstrom et al. (1980) also published warnings regarding the use of Thimerosal, this time in vaccines: "Reactions can be expected in such a high percentage of Merthiolate-sensitive persons that Merthiolate in vaccines should be replaced by another antibacterial agent" (p. 241).

Heyworth (1982) described:

> During a study of the properties of two antisera which had been prepared against human lymphoid cells, the present author found that one of the antisera was cytotoxic to lymphoid and non-lymphoid cells(.) . . . This effect was attributable to the organomercurial compound Merthiolate, which had been added to the (antilymphocyte serum) ALS as a preservative . . . In the opinion of the present author, Merthiolate should no longer be added to ALS or other materials which are intended for use in human subjects. Tissue accumulation of mercury has been observed. (p. 91)

It was reported in 1983, in an article titled "Mercury Poisoning in Child Treated with Aqueous Merthiolate," that administration of Thimerosal resulted in a child dying from mercury toxicity (Anonymous, 1983). The article stated, "The Ohio Board of Pharmacy has received an investigative report from the Ohio Department of Health's Division of Epidemiology regarding the death of a 21-month old child due to mercury poisoning. The investigation strongly implicated the Thimerosal solution as 'the source of mercury' that subsequently resulted in the child's death since no other source could be identified" (p. 523).

Kravchenko et al. (1983) questioned the use of Thimerosal in vaccines and its inexplicable acceptance in light of mounting scientific evidence demonstrating its inherent toxicity. These researchers found: "Our experiments show that Merthiolate in 1:10,000 titer can not only damage cells in culture but also change their properties. . . Increased sensitivity to this mercury compound has been frequently noted in medical literature, and deserves particularly close attention. Although there are numerous clinical studies confirming Merthiolate's damaging action on humans, [medical and biological preparations] MBP preservation with it continues and is even recommended by WHO" (p. 87–92). In regard to the use of Thimerosal in vaccines, the researchers concluded, "All of the above show that Merthiolate usage for MBP manufacturing is inadmissible, especially in pediatrics . . . . Vaccines must contain only specific substances, free of ballast. There is no way that cell damage can cause not harmful sequelae in the body" (p. 87–92).

Hekkens et al. (1983) undertook an evaluation of the effectiveness of some preservatives in inactivated human vaccines by application of the test described in the United States Pharmacopoeia (USP) XIX. These researchers described that five recommended strains as well as three strains isolated from vaccines were used as test strains. It was observed that vaccines preserved with Thimerosal did not fully meet the requirements for a vaccine preservative according to the criteria established by the USP XIX.

Royhans et al. (1984) reported on mercury toxicity following pediatric Thimerosal ear irrigations. With regard to the danger posed by mercurials, the researchers were expansive in stating:

> Although aqueous Merthiolate has been used for years as a topical antiseptic, a recent review of its use by the Food and Drug Administration resulted in its classification as 'less than effective.' Furthermore, two of the ingredients (Thimerosal and borate) in Merthiolate are toxic if absorbed or injected . . . Symptoms of organic mercury poisoning chiefly involve the central nervous system, including paresthesia of the mouth, lips, tongue, and extremities; speech disorders, with difficulty in articulating words; difficulty in swallowing; salivation; neurasthenia; inability to recall basic information; emotional instability; ataxia; clumsiness; stupor; and coma . . . Reactions to mercury depend to a large extent on the form of the chemical agent; its absorption, storage, and excretion; duration of exposure; and individual susceptibility. Both inorganic and dissociable organic mercurials appear to act by the same mechanism. Mercury ion reacts with sulfhydryl groups to form mercaptides, which inactivate sulfhydryl enzymes and interfere with cellular metabolism . . . The blood–brain barrier, is also more permeable to organic than inorganic mercury. There are definite individual differences in sensitivity to the effects of mercurials. Some patients tolerate prolonged exposure without symptoms; others have significant systemic signs and neurological disability with much less exposure. The mercury in Merthiolate is a thiosalicylate compound that is converted to inorganic mercury more rapidly than is methyl mercury. The organic compound itself is also easily absorbable, and undergoes widespread tissue distribution. Toxicity may be related both to the biotransformation into inorganic mercury and to the unchanged compound, both of which cause degenerative changes in the brain, especially in the visual cortex and cerebellum, and proliferative changes throughout the cerebellar cortex. (p. 311–312)

Winship (1985, p. 171) reported, "Multi-dose vaccines and allergy-testing extracts contain a mercurial preservative, usually 0.01% Thimerosal, and may present problems occasionally in practice. It is, therefore, now accepted that multi-dose injection preparations are undesirable and that preservatives should not be present in unit-dose preparations."

Stetler et al. (1985) from the U.S. CDC also evaluated the use of Thimerosal as a preservative in vaccines and found it to be unsatisfactory. The authors reported that Thimerosal was ineffective as a vaccine preservative, and that giving more mercury than was present in a single Thimerosal-containing vaccine might pose a health hazard to vaccine recipients. Evaluating the effectiveness of Thimerosal as a preservative in vaccines, the authors stated: "Laboratory experiments in this investigation have shown up to 2 weeks' survival of at least one strain of group A Streptococcus in multidose DTP (Diphtheria-Tetanus-Pertussis) vials. The manufacturer's preservative effectiveness tests showed that at 4°C, 4.5% of the challenge Streptococcus survived 14 d after inoculation into a multi-dose DTP vaccine vial. At currently used concentrations, Thimerosal is not an ideal preservative" (p. 302–303). The authors also made specific reference to the toxicity of Thimerosal: "However, because Thimerosal is an organic mercurial compound, higher concentrations might reduce vaccine potency or pose a health hazard to recipients" (p. 303). Their recommendations regarding the use of multi-dose vials with a Thimerosal preservative were as follows: "The Thimerosal preservative present in DTP vaccine requires substantial time to kill organisms and cannot be relied upon to prevent transmission of bacteria under conditions of practice when a vial is used over a short period. Instead, the most important means of preventing abscesses secondary to DTP vaccination is to prevent contamination by careful attention to sterile technique" (p. 303).

Furthermore, Cox and Forsyth (1988) recommended, "However, severe reactions to thiomersal demonstrate a need for vaccines with an alternative preservative" (p. 229).

Digar et al. (1987) expanded the knowledge base regarding the marked toxicity of Thimerosal to the developing fetus. The researchers reported:

> A single dose of 0.1 mg of Ethyl-mercury-thiosalicylate (Thimerosal) was injected into the yolk sac of chick embryos . . . Embryos were collected . . . It was found that 0.1 mg dose of Thimerosal was lethal in 46.46%. Gross malformations like syndactyly, thinning of the abdominal wall, visceroptosis and scanty feather, during Organogensis as well as in the later period, have been noted in 36.03% . . . Significant change in the weight of embryo, crown–rump length, body and wing lengths were also observed . . . However, there was no gross reduction in the size of brain as compared to that of the control. The high incidence of lethality and malformations prove that organic mercury was transmitted from the yolk sac to the embryo. The deleterious effects of mercurials on cells and tissues seem to be due to action on a wide spectrum of enzymes by the organic mercury both on the surface and within the cell. The enzymes particularly involved are−Na−K activated ATPase and also sulfhydryl groups. Goldwater reported that mercury disrupts the normal function of mitochondria and lysosomes. (p. 153, 157)

Withrow and his colleagues (1989), from the U.S. FDA, in keeping with the expanding circle of scientists and physicians expressing ever-increasing concerns in regard to the use of Thimerosal as a preservative, evaluated the cytotoxicity and mutagenicity of Thimerosal at preservative levels in a tissue culture system. These researchers reported:

> It is known that Thimerosal . . . present in lens care solutions sometimes cause(s) ocular irritation in contact lens users. For example, Coward et al. (1984) reported that 33% of patients using lens care solutions with Thimerosal . . . experienced solution intolerance . . . In vitro studies have shown that preservatives are toxic to cultured human and rat corneal epithelial cells and toxic to isolated rabbit corneas, and to intact rabbit eyes. (p. 385)

Additionally, these researchers described the impact of Thimerosal at the cellular level:

> Cell survival and mutagenesis were measured using the L5178Y mouse lymphoma (TK +/–) system. Cells were exposed to varying amounts of preservatives for 1 h at 37°C, and then aliquots were

> irradiated with UVA radiation (during the exposure to the preservative). Cells were then assayed for survival, and for mutagenesis at the thymidine kinase (TK) locus. In concentrations commonly found in ophthalmic solutions . . . Thimerosal (was) toxic to cells, and Thimerosal was slightly mutagenic. When cells were exposed to preservative and UVA radiation. . .the mutagenic activity of Thimerosal was enhanced. (p. 385)

Nascimento et al. (1990) not only reported on a death following Thimerosal ingestion but also warned of the widespread danger which Thimerosal posed. Specifically, they reported, "A case of mercurial poisoning caused by ingestion of an organic mercurial compound, Thimerosal, found in local antiseptic solutions. The clinical picture consisted of grave neurological symptoms which were not reversed by penicillamine and resin administration despite rapid plasma level reduction of mercury. We call attention to this case because of the widespread availability of antiseptic solutions containing mercurial compounds" (p. 218).

Aberer (1991) reviewed the continued use of mercury in medicine. In his article, Aberer (1991) was comprehensive in declaring the extent of the problem that Thimerosal represented in pharmaceutical products: "The presence of mercury in over-the-counter drugs for the eye, ear, nose, throat, and skin; in bleaching creams; as preservative in cosmetics, tooth pastes, lens solutions, vaccines, allergy test and immuno-therapy solutions, in antiseptics, disinfectants, and contraceptives; in fungicides and herbicides; in dental fillings and thermometers; and many other products, makes it a ubiquitous source of danger" (p. 150). He then went on to document the systemic failure to remove this toxin from pharmaceutical products, "Despite calls for abandonment and a general prohibition in 1967, mercury is still listed in many pharmacopoeias, including that of the United States . . . Thus mercury is still much more frequently used than is generally believed. This seems incomprehensible because side effects are not only potentially disastrous but also numerous and well documented." In describing the numerous and well-documented side effects of the use of mercury in medicine, he stated that these included "Neurologic and psychiatric symptoms, renal toxicity, erythroderma, and other signs of poisoning," (p. 150) and furthermore, "Knowledge of all these side effects has been available for some time" (p. 150). He concluded by arguing, "Recommendations not to use mercury salts in children or only on prescription are insufficient. Removal from textbooks seems overdue . . . However, calls for their abandonment (as early as 1960) or restricted use have not sufficed. Only a general ban and their removal from the pharmacopoeias will be effective in stopping the use of these dangerous, outmoded substances" (p. 150).

Brunner et al. (1991) evaluated the effects of Thimerosal in an in vitro porcine brain tubulin assembly assay. These researchers examined the influence of Thimerosal on different parameters [lag-phase, polymerization velocity, end absorption (steady-state level), reversibility, and influence on disassembly at 4°C]. It was observed that low concentrations of Thimerosal led to a rapid inhibition of tubulin assembly and disassembly of microtubules.

Additionally, Seal et al. (1991), in their article on the case against Thimerosal, concluded, "Thimerosal is a weak antibacterial agent that is rapidly broken down to products, including ethylmercury residues, which are neurotoxic. Its role as a preservative in vaccines has been questioned, and the pharmaceutical industry considers its use as historical" (p. 315).

Hilleman (1991) from the Merck Vaccine Task Force expressed a newly initiated internal concern over the mercury exposure infants were receiving through standard immunizations. It was expressed:

> PROBLEM: The regulatory control agencies in some countries, particularly Scandinavia (especially Sweden), but also U.K., Japan, and Switzerland, have expressed concern for Thimerosal, a mercurial preservative, in vaccines . . . PUTTING THIS INTO PERSPECTIVE: For Babies: The 25 μg of mercury in a single 0.5 mL dose and extrapolated to a 6 lb. baby would be 25× the adjusted Swedish daily allowance of 1.0 μg for a baby of that size. The total mercury burden in a baby is unknown but it has been stated that the blood level of a newborn may exceed that of the mother. If 8 doses of Thimerosal-containing vaccine were given in the first 6 months of life (3 DPT, 2 HIB, and 3 Hepatitis B) 200 μg of mercury given, say to an average size of 12 lbs., would be about 87X the Swedish daily allowance of 2.3 μg of mercury for a baby of that size. When viewed in this way, the mercury load appears rather large. (p. 1, 5)

Lowe and Southern (1994) evaluated the antimicrobial action of various preservatives for vaccines. They described, "The preservative most commonly used is Thiomersal. Other preservatives are being evaluated because: (i) this material has become difficult to obtain; (ii) the use of mercury-containing compounds in medicinal products is considered potentially harmful; and (iii) it has been found that some vaccine components are unstable in the presence of this material" (p. 115). In light of these facts, the researchers undertook a series of experiments comparing the antimicrobial activity of phenoxyethanol with Thimerosal in diphtheria, tetanus, and pertussis (adsorbed) vaccine. It was observed, "Both chemicals were equally effective in inactivating challenge doses of Gram-negative and Gram-positive micro-organisms, as well as yeast" (p. 915). In significant contrast to their concerns regarding the potentially harmful effect of mercury-containing compounds, Lowe and Southern (1994) noted, "the low toxicity of phenoxyethanol in children has been reported" (p. 915).

Lowell et al. (1996), from the Washington University School of Medicine, made overt the association between Thimerosal and mercury poisoning by evaluating the adverse effects resulting from administration of Thimerosal-containing hepatitis B immunoglobulin (HBIG). They reported:

> Preparations of HBIG use Thimerosal (a mercury derivative) as a preservative. We encountered mercury toxicity, in a patient who received high-dose immunoprophylaxis . . . HBIG preparations contain Thimerosal as a preservative, which contains 49% organically bound mercury. Previous reports have demonstrated that administration of Thimerosal-containing products may lead to mercury poisoning . . . Physicians should suspect mercury toxicity in patients receiving high-dose HBIG. (p. 480)

Overshadowing the recorded concerns of independent researchers and pharmaceutical representatives is the critical and unheeded recommendation that pregnant women and newborn children should be protected from the potential neurotoxic effect of mercury-containing pharmaceuticals issued internally within the FDA. In August 1998, a U.S. FDA internal "Point Paper" was prepared for the Maternal Immunization Working Group. This document officially recommended, "For investigational vaccines indicated for maternal immunization, the use of single dose vials should be required to avoid the need of preservative in multi-dose vials. . . Of concern here is the potential neurotoxic effect of mercury especially when considering cumulative doses of this component in early infancy" (Subcommittee on Human Rights and Wellness, 2003, p. 36).

CONCLUSION

The high order of toxicity from Thimerosal and its ethylmercury breakdown product has been known and published for decades. Nonetheless, Thimerosal remains in the drug supply, especially in various vaccines manufactured both for the United States and globally. The ubiquitous and largely unchecked place of Thimerosal in pharmaceutical products, therefore, represents a medical crisis in the modern day. Reforms in the manufacture and the licensing of vaccines and other drugs, which should have been accomplished proactively, had anyone properly assessed their mercury content, must now be conducted, reactively, under significant systemic stress. With no warning, recall, or ban of mercury in vaccines and other drugs as of yet, the victim of this mandated, unwarranted, and massive mercury exposure is still an unsuspecting public, and most especially its unborn and newborn children.

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