Silent Latency Periods in Methylmercury Poisoning and in Neurodegenerative Disease

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This article discusses three examples of delay (latency) in the appearance of signs and symptoms of poisoning after exposure to methylmercury. First, a case is presented of a 150-day delay period before the clinical manifestations of brain damage after a single brief (<1 day) exposure to dimethylmercury. The second example is taken from the Iraq outbreak of methylmercury poisoning in which the victims consumed contaminated bread for several weeks without any ill effects. Indeed, signs of poisoning did not appear until weeks or months after exposure stopped. The last example is drawn from observations on nonhuman primates and from the sequelae of the Minamata, Japan, outbreak in which low chronic doses of methylmercury may not have produced observable behavioral effects for periods of time measured in years. The mechanisms of these latency periods are discussed for both acute and chronic exposures. Parallels are drawn with other diseases that affect the central nervous system, such as Parkinson disease and post-polio syndrome, that also reflect the delayed appearance of central nervous system damage. *Key words:* hormesis, latency, methylmercury, neurodegenerative disease, neurotoxicology. *Environ Health Perspect* 110(suppl 5):851–854 (2002).
http://ehpnet1.niehs.nih.gov/docs/2002/suppl-5/851-854weiss/abstract.html

A recent case of methylmercury poisoning provided a dramatic example of a long latency period between exposure and the onset of clinical symptoms of poisoning (*1*). The victim was briefly exposed to dimethylmercury in attempting to pipette this liquid form of mercury. Although the transfer took place in a fume hood, and the victim wore protective gloves, she was exposed to an amount of methylmercury that would ultimately prove fatal. Despite this high single dose, the first symptoms of poisoning did not occur until 150 days later.

The analysis of a single strand of scalp hair revealed the progression of mercury levels over the entire period from exposure to her ultimate demise (Figure 1). The data points were fitted with a pharmacokinetic model consisting of a rising and a falling phase, each characterized by a single exponential term. The rising phase had a half-time of approximately 6 days. This period likely represents the time needed for the metabolic conversion of dimethylmercury to monomethylmercury, as shown to occur in animal studies (*2*). Monomethylmercury is known to be avidly accumulated into scalp hair. Once incorporated into the formed elements of the hair strand, its concentration remains constant. The concentration in the newly formed hair bears a constant ratio to the simultaneous blood level (*3*).

The falling phase is represented by a smooth curve with a half-time of about 74 days, consistent with methylmercury kinetics in humans (*4*). This curve indicates that no subsequent exposure took place, in agreement with the clinical records. At the 150-day time point, when symptoms first appeared, the mercury level had dropped by a factor of four, corresponding to the 74-day half-time. During this period, the patient experienced no ill effects and pursued her normal duties as a professor of chemistry at Dartmouth College. The exposure took place in the month of August. It was not until the end of December that the first ill effects appeared. Thereafter, the full neurological syndrome of severe methylmercury poisoning rapidly developed. After just 2 weeks the patient was severely affected and remained in this condition until her death a few months later. How do we explain the 150-day latency period followed by a sudden onset of severe methylmercury poisoning?

Latencies in Acute Methylmercury Poisoning

The neuropathology of methylmercury is well described from previous cases (*5*). Focal anatomical areas are affected (Figure 2). For example, the small granule cells of the cerebellum are destroyed, but the neighboring Purkinje cells are relatively unaffected. The signs of incoordination (ataxia), typical of severe poisoning, are probably due to damage to this area of the brain. Constriction of the visual fields results from the loss of neurons from the visual cortex.

The severity of the damage is related to the magnitude of the dose, as illustrated in Figure 3. These data are taken from an outbreak of poisoning in the winter of 1971–1972 in rural Iraq, where farmers and their families ingested homemade bread made from seed wheat treated with a methylmercury fungicide (*7*). As the levels of methylmercury in hair increase, the earliest symptom, a tingling sensation (paresthesia), appears. With rising hair levels, increasing proportions of the population are affected. Ataxia is the next adverse effect to appear, followed by difficulty in pronouncing words (dysarthria), deafness, and ultimately death. The peak hair level of about 1,000 ppm in the Dartmouth case is consistent with the finding in Iraq, where fatalities appeared at hair levels above 800 ppm.

It is generally assumed that, as the dose increases, more damage to the brain must take place. If the severity of damage is dose dependent, is the latency period also dose dependent? A typical sequence of the development of poisoning in Iraq is shown in Figure 4. The contaminated bread was ingested over a period of weeks. Many individuals stopped eating the bread as a result of warnings from the public health authorities. This was followed by a latency period before the onset of symptoms. Bakir et al. (*7*) reported that the length of the latency period showed no decrease with rising blood levels (Table 1). The average latency periods fell within a range of approximately 16–38 days. In the Dartmouth case described previously, the patient had a maximum hair level (Figure 1) equal to the highest levels reported in Iraq (Figure 3) and exhibited the longest latency period. This finding is not what one would expect intuitively. For example, if mercury were reacting with a target molecule to produce its toxic effects, one would expect that the higher the level of mercury, the sooner the damage would appear.

Perhaps the latency period is due to the slow production and accumulation of a toxic metabolite. For example, methylmercury is known to be converted to divalent inorganic mercury in the brain over periods of months

This article is part of the monograph *Molecular Mechanisms of Metal Toxicity and Carcinogenicity.*

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We acknowledge support in part from National Institute of Environmental Health Sciences grants R01 ES10219, R01 ES08442, R01 ES08958, and P30 ES01247. We also acknowledge the Food and Drug Administration, the U.S. Environmental Protection Agency, and the Agency for Toxic Substances and Disease Registry.

Received 31 January 2002; accepted 20 May 2002.

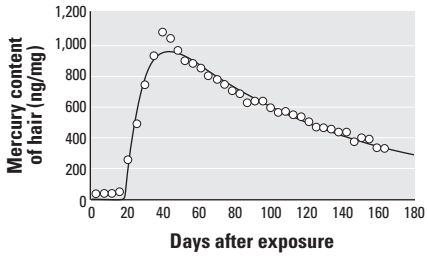

Figure 1. The concentration of mercury in a single strand of hair collected from a person exposed to dimethylmercury at day 0. Reproduced from Nierenberg et al. (*1*). ©1998 Massachusetts Medical Society. All rights reserved.

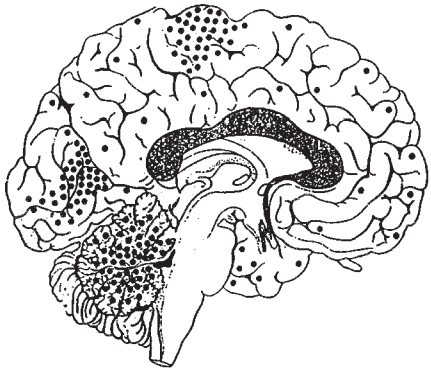

Figure 2. Focal anatomical areas of an adult brain affected by methylmercury. The black circles show the localization and distribution of pathological changes. Adapted from Tsubaki and Irukayama (*6*).

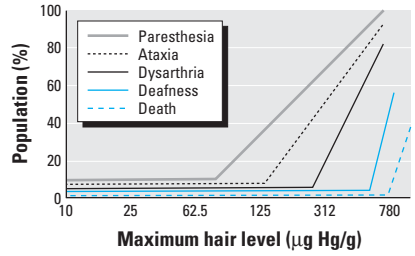

Figure 3. The frequency of signs and symptoms of methylmercury poisoning in a population exposed in the Iraq outbreak. Modified from Bakir et al. (*7*).

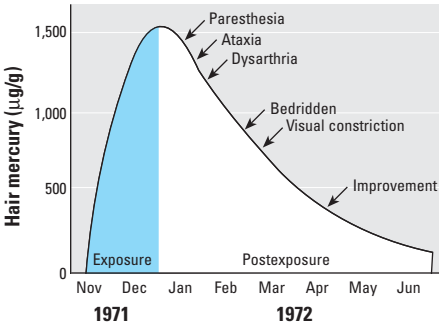

Figure 4. The sequence of appearance of signs and symptoms of methylmercury poisoning in a victim in the Iraq outbreak. Reproduced from Clarkson (*8*) with permission of the *American Journal of Clinical Nutrition. © Am J Clin Nutri.* American Society for Clinical Nutrition.

(*9*). However, as illustrated in Figure 5, one would expect the buildup of inorganic mercury to be faster at higher levels of methylmercury, resulting in a shorter latency period. It is possible that the rate of conversion to inorganic mercury is rate limited and therefore occurs at a steady rate independent of the level of methylmercury. However, we should also have to assume that inorganic mercury is the proximate toxic agent in methylmercury poisoning. This assumption is contrary to evidence in the literature (*10*).

Berlin et al. (*11*) noted that the distribution of methylmercury in the brain of squirrel monkeys slowly changed over a 1-month period. The change in distribution seemed to be correlated with the onset of toxic effects. However, the authors raised the caveat that "it cannot be determined from the limited material whether the redistribution causes the toxic effects or results from it." Certainly, it is difficult to understand how a toxic redistribution would take as long as 150 days with brain levels of methylmercury falling during this period.

It is as if methylmercury were acting as a trigger. Once its concentration in brain exceeds a certain threshold level, a slow process would be initiated that ultimately results in cell death. The rapid development of the full syndrome of poisoning suggests two possible processes. Under one scenario, this process takes roughly the same amount of time for the different neuronal cells affected. The nature of this process is unknown. It might, for example, be the accumulation of a toxic protein, as is the case in Alzheimer disease but taking place over months instead of years. An alternate possibility, discussed in detail later in this article, is that the population of neuronal cells embodies a statistical distribution of susceptibility. In this scenario, the more susceptible cells succumb first. As they die, surviving cells assume their function, but eventually, because of the increased functional load and metabolic stress, these cells also succumb. At some point, the neuronal population has exhausted its capacity to compensate for the cell loss and clinical signs rapidly erupt.

It has been suggested (*12*) that methylmercury might trigger the synthesis of a protective molecule. For example, the synthesis of glutathione can be induced by methylmercury in the brains of rodents (*13*). This molecule is known to be protective against methylmercury damage to the brain (*14*). However, it does not explain the continuation of the induction process for a 150-day period. A mechanistic explanation of the latency period in severe acute poisoning remains elusive.

Latency after Low-Level Chronic Exposure

Much longer latency periods are associated with low-level chronic exposure to methylmercury. Latency periods extending for several years are illustrated in Figure 6 for both human and nonhuman primates. Rice (*15*) demonstrated that monkeys receiving a low daily dose of methylmercury for the first 7 years of life developed no signs of poisoning until 13 years of age, that is, after a latency period of 6 years. The adverse effects were mild, unlike the severe intoxications discussed above, and consisted mainly of impaired dexterity and clumsiness in handling items of food. Latency periods as long as 15 years have been reported after the Minamata outbreak [for details, see Igata (*16*)].

Evans et al. (*17*) conducted a long-term study on nonhuman primates in which the desired blood levels were quickly established with priming doses and then maintained for periods up to 1,400 days by weekly administration. This study clearly demonstrated that the latency period was dose dependent (Figure 7). The length of the latency period decreased with increasing blood levels, unlike the pattern seen after acute severe doses.

A plausible mechanism for this second type of latency period comes from a model offered by Weiss and Simon (*18*). They proposed that the normal loss of cells due to aging over some portion of the human life span can be accelerated by neurotoxic agents (Figure 8). The model demonstrates how even a slightly accelerated rate of loss can lead to a significant reduction of cell number and premature brain aging over a period of decades.

This concept may be applied to explain the second type of latency period for methylmercury. A toxic dose of mercury will cause

Table 1. Blood levels of mercury, period of ingestion of contaminated bread, and the length of latency period.

Concentration of mercury in blood (ng/mL)	Mean period of ingestion (days)	Mean latency period (days)	Number of persons exposed
0–100	43	—	21
101–500	43	—	19
501–1,000	43	16	19
1,001–2,000	41	18	17
2,001–3,000	55	26	25
3,001–4,000	58	32	17

Length of latency period is time between the end of contaminated bread consumption and the appearance of signs and symptoms of methylmercury poisoning. Data from Bakir et al. (*7*).

an initial cell loss, which may or may not reduce the number of target cells to the point at which overt symptoms appear. Over time, the aging process will further reduce the number of cells until those that remain are too few to sustain function, and overt effects then erupt. In this situation the higher the initial dose, the greater the loss of cells due to the action of mercury. This will in turn reduce the latency period due to aging. This model explains the dose dependency of the second type of latency period.

The outcome of this "aging" latency period will be affected by the degree of cell loss after the initial insult. The aging process should result in increasingly severe effects as cell number continues to fall. Such an outcome is consistent with the findings of Evans et al. (*17*) in nonhuman primates and in the human cases from Minamata.

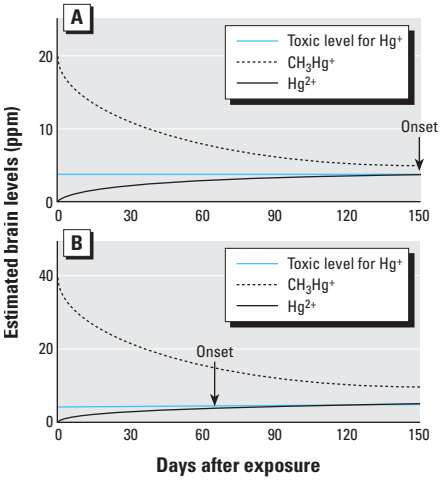

Figure 5. The rate of production of inorganic mercury (Hg^{2+}) from methylmercury (CH_3Hg^+) in the brain after a (*A*) low and (*B*) high dose. The curves are theoretical based on the assumption that the rate of production of inorganic mercury is a first-order process.

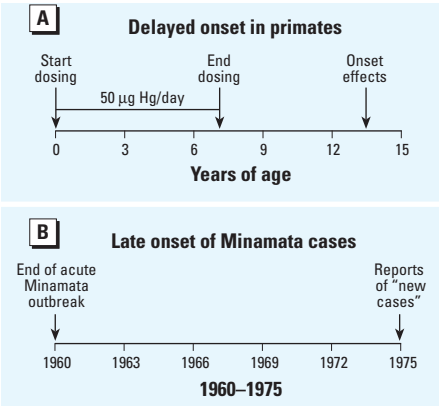

Figure 6. The late onset of methylmercury poisoning in nonhuman primates and in humans after exposure to methylmercury in Minamata. Based on (*A*) Rice (*15*) and (*B*) Igata (*16*).

Additional Possibilities and Processes

We must also entertain the possibility of another kind of process that may account for the long-latency phenomenon seen with the Dartmouth patient described in the introductory remarks. To some degree, it mimics the process presumed to underlie Parkinson disease. Most observers agree that the appearance of clinical signs is merely the ultimate phase of a neurodegenerative process whose inception might even be traced to events occurring during early development (*19*). The clinical signs are believed to emerge after the death of 60–90% of the pigmented, dopamine-producing cells in the substantia nigra pars compacta. The long latency is attributed to the ability of the remaining cells to compensate for the functions of the vanished cells (*20*). Figure 9 models such a process. It depicts the relationship between the number of cells remaining and the amount of neurotransmitter (or other functional output) required of each remaining cell to compensate for the lost cells. The empirical data indicate that such a compensatory process does occur with Parkinson disease, but that eventually, of course, it breaks down. The Dartmouth case of dimethylmercury poisoning described above may reflect such a process. During the 5 months preceding the onset of clinical signs, it is conceivable that brain cells were undergoing continuous destruction. Only after the compensatory mechanisms began to fail under their burden, we might presume, did the extent of destruction assert itself.

The breakdown process itself, moreover, might have engendered further, independent damage. Table 2 outlines a hypothetical sequence of events analogous to what some observers believe applies to Parkinson disease and to post-polio syndrome. As the surviving cells increase neurotransmitter output or develop additional synaptic connections to compensate for those no longer functional, they may also produce greater amounts of toxic metabolic products or stress the parent cells, so that the entire process becomes trapped in a positive feedback loop.

Other explanations, which do not exclude the one described above, may also be at work. As pointed out earlier, nerve cells are not all equally vulnerable and display a population distribution of susceptibility. We can assume that the more susceptible cells (perhaps the smaller ones) die first. The less susceptible, remaining cells should be able to take on the roles of those no longer functioning. The

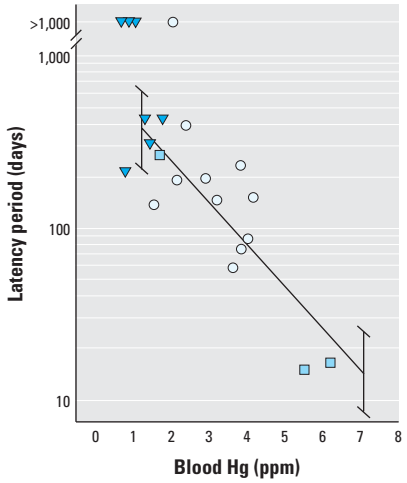

Figure 7. The length of the latency period as a function of steady-state blood levels in nonhuman primates dosed with methylmercury. Inverted triangles represent squirrel monkeys from Berlin et al. (*11*). Circles represent macaque monkeys from Evans et al. (*17*). Squares represent macaques from Shaw et al. as quoted by Evans et al. (*17*). From Evans et al. (*17*) with permission of Academic Press.

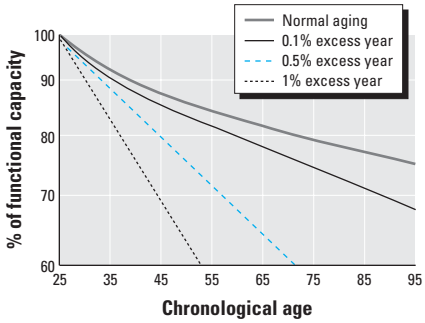

Figure 8. The loss in functional capacity of the brain from 25 years of age onward. The uppermost curve depicts "normal" aging. The lower three curves depict the consequence of a slight increase in the rate of loss. From Weiss and Simon (*18*) with permission of Plenum Press.

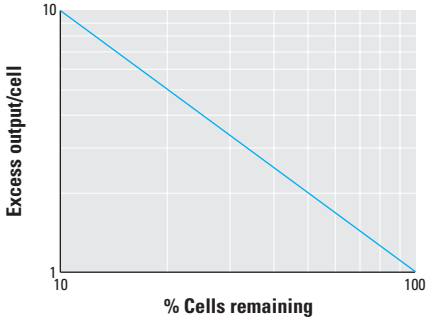

Figure 9. Compensation for cell loss. The figure depicts the relationship between the number of cells remaining and the amount of neurotransmitter (or other functional output) required of each remaining cell to compensate for the lost cells.

Table 2. Components of a multistage neurodegenerative process.

Erosion of cell numbers
Increased transmitter production per cell
Accumulation of toxic products of synthesis
Functional exhaustion
Death

brain is built with considerable redundancy; even adult brains, which presumably lack the suppleness of developing brains, often make remarkable recoveries after strokes of considerable extent. Post-polio syndrome is perhaps one example of such a selective destruction. Decades after having apparently recovered from an acute poliomyelitis infection, those affected begin to experience a reappearance of the original motor deficits. Most observers credit this phenomenon to "overworked" cells in the spinal cord.

Another example of late onset also comes from polio. Martyn et al. (*21*) correlated the incidence of amyotrophic lateral sclerosis (motoneuron disease) in U.K. counties during the 1960s with the incidence of polio in the 1930s. They found a significant relationship and explained it as follows:

> We suggest that motoneuron disease is a rare and delayed consequence of an infection with poliovirus that affects the central nervous system and causes loss of motoneurons but is not usually severe enough to cause motor symptoms or paralysis at the time of the acute illness.

Common Themes

We have reviewed three varieties of outcomes, characterized by three different patterns of delayed neurotoxicity between exposure and the onset of detectable signs. The first is exemplified by the puzzling case of the chemist whose brief exposure to an eventually fatal dose of dimethylmercury preceded the emergence of clinical signs by 150 days. The puzzle arises from the prolonged latency before the onset of unequivocal neurotoxicity, which covered a period during which blood and hair levels fell continuously. The dose did not, in this instance, make the poison, so to speak, in apparent violation of a cherished principle of traditional toxicology.

A second pattern is illustrated by neurodegenerative disorders such as Parkinson disease and post-polio syndrome and exemplified, too, by low-level chronic exposure to methylmercury. In these instances, we assume an underlying pathological process whose consequences remain submerged because of the innate redundancy of the brain. Only after the compensatory mechanisms have been overwhelmed, sometimes in combination with spontaneous loss of function due to aging, do the overt signs of damage become evident.

The third pattern is exemplified by the mass chemical disaster in Iraq in the winter of 1971–1972. Here, seed wheat treated with a methylmercury fungicide was distributed to a rural population that then used it to make homemade bread and triggered an epidemic of poisoning striking tens of thousands of individuals. From tracking the victims, whose exposures extended over a period of about 3 months, the kind of paradoxical result seen in the case of the Dartmouth chemist was also seen in this population: higher blood levels of mercury, despite inflicting more serious damage, also took longer to produce visible signs than did lower blood and hair levels.

Conclusions

The question we posed is whether similar mechanisms underlie all three patterns. The commonalities are obvious: manifestations of damage emerge only after compensatory processes have been exhausted. The unresolved conundrum comes from the Iraq example, in which the latency period tended to lengthen with increasing blood levels. Such a phenomenon is not as uncommon as it seems. Cory-Slechta et al. (*22*), for example, observed that higher doses of lead acetate to rats trained on an operant procedure evoked longer latencies to diminished performance than did lower doses. One possible although speculative explanation may be related to a phenomenon gaining wider recognition in toxicology: namely, nonmonotonic dose–response relationships. Several recent reviews [e.g., Calabrese and Baldwin (*23*)] have pointed out the frequent occurrence of U-shaped dose–response functions in the life sciences. Their shape conflicts with the traditional assumption of direct dose–response relationships. Several possibilities have been offered to account for the shape of these functions. Most rely on the concept of hormesis, which asserts that low-level exposures stimulate compensatory processes that, in essence, overshoot and confer an added measure of protection. But the mirror image of hormesis can also prevail, giving rise to a situation in which only high-level exposures invoke compensatory processes. In this instance, low-level exposures are more likely than high-level exposures to show evidence of adverse effects or, at least, to show them more rapidly. Such phenomena have been observed with endocrine disruptors [e.g., (*24*)].

If any lesson is to be derived from the examples discussed in this article, it is that the conventional tenets of toxicology need to be observed with a considerable degree of skepticism. We should be convinced, not by dogma, but by a deep understanding of mechanisms.

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