EUR. J. ONCOL.; Vol. 21, n. 1, pp. 51-60, 2016

Learning from Bernardino Ramazzini, a tribute to the Magister from Carpi and to the Fellows of the Collegium Ramazzini

Philippe Grandjean

Department of Public Health, University of Southern Denmark, Odense, Denmark; and Department of Environmental Health, Harvard T.H.Chan School of Public Health, Boston, USA

We are pleased to publish the full text of the 2015 Ramazzini Lecture which was presented by Professor Philippe Grandjean, recipient of the 2015 Ramazzini Award, on the occasion of the conferment ceremony whith took place in Carpi, Italy on October 24, 2015

Summary. Bernardino Ramazzini became famous as the author of the first textbook on occupational medicine, but his lasting importance to medicine and public health also includes his logical approach to medical diagnosis and prevention. While relying on background evidence, he explored the patient's environment and learned from the victim before recommending preventive intervention. This approach was later adopted by Irving J. Selikoff, and it has helped gaining insight into modern impacts of environmental pollution. A prime example is mercury, a hazard that already Ramazzini examined. Recent experience on this pollutant has disclosed that epidemiological findings easily underestimate the extent of exposure-related adverse effects. In their publications, scientists often use hedged language that may be misunderstood and misused, especially by vested interests. Mounting scientific evidence on mercury and other exposures has led to the recognition of the developmental origin of health and disease as an important paradigm that emphasizes the extreme vulnerability during early life-stages, where especially the developing brain is now known to be a key target organ for neurotoxicants, such as methylmercury. Had Bernardino Ramazzini been around today, he would have used his logical approach to focus on the health of the next generation.

Key words: clinical examination, environmental exposure, epidemiology, etiology, methylmercury compounds, occupational disease

«La lezione di Bernardino Ramazzini. Un tributo al Maestro di Carpi ed ai Fellows del Collegium Ramazzini»

Riassunto. Bernardino Ramazzini diventò famoso come autore del primo libro sulla medicina del lavoro, ma il suo duraturo contributo alla medicina e alla sanità pubblica gli è riconosciuto anche per il suo approccio logico alla diagnosi clinica ed alla prevenzione. Pur tenendo in considerazione l'evidenza del quadro clinico, egli prendeva in esame l'ambiente del paziente e da esso traeva insegnamento prima di consigliare un intervento preventivo. Questo approccio fu adottato più tardi anche da Irving J. Selikoff, e ciò lo aiutava ad approfondire l'impatto dell'inquinamento ambientale. Un primo esempio è il mercurio, un pericolo che già Ramazzini aveva preso in esame. L'esperienza recente relativa a questo inquinante ha evidenziato che i dati epidemiologici francamente sottostimano il livello espositivo correlato agli effetti dannosi. Nelle loro pubblicazioni, gli scien-

ziati spesso usano un linguaggio elusivo che può essere incomprensibile e mal interpretato, specialmente per interessi acquisiti. L'aumentare delle evidenze scientifiche sul mercurio e su altri tipi di esposizione hanno dimostrato che il periodo dello sviluppo può essere l'origine della salute e delle malattie, un importante esempio che mette in evidenza l'estrema vulnerabilità dei primi momenti della vita, durante i quali, specialmente per quanto riguarda lo sviluppo cerebrale, è ora riconosciuto come "organo bersaglio" per sostanze neurotossiche, come il metilmercurio. Se Bernardino Ramazzini fosse qui oggi avrebbe utilizzato il suo approccio logico per concentrarsi sulla salute delle prossime generazioni.

Parole chiave: esame clinico, esposizione ambientale, epidemiologia, eziologia, composti di metilmercurio, malattie ambientali

Abbreviations

DOHAD, Developmental Origin of Health And Disease; EPA, Environmental Protection Agency

Introduction

Bernardino Ramazzini (1633-1714) was born in the city of Carpi and was educated as a physician. He became famous as the author of the first textbook on occupational medicine (1) and is therefore considered the father of the specialty (2-4). While *De morbis artificum diatriba* ("Diseases of Workers") served as a medical textbook for close to two centuries, less attention has been paid to his logical approach to medicine and prevention. Thus, while his treatise has been superseded by other textbooks on work-related diseases, his medical logic still provides inspiration for practitioners and scientists in the field.

As was common at the time, Ramazzini relied on the teachings of Hippocrates and less remote predecessors, and he famously extended the clinical examination: "I may venture to add one more question: what occupation does he follow?" (from the translation by Wilmer Cave Wright (1)). Ramazzini encouraged an active exploration of the patient's circumstances: "I for one have done all that lay in my power, and have not thought it beneath me to step into workshops of the meaner sort now and again and study the obscure operations of mechanical arts." Most notably, he then advised prudent action: "...to secure good conditions for workers… the art of medicine should contribute its portion for the benefit and relief... [We] ought to show peculiar zeal...in taking precautions for their safety." In short, "It is better to prevent than to cure…"

Beyond the linking of certain trades to particular diseases, Ramazzini therefore deserves attention for his systematic approach to the clinical presentation of diseases and their relationship to causal factors (4, 5). The three steps to dealing with occupational diseases relied on existing background knowledge, which he actively complemented by learning from the patient and examining the patient's environment, followed by specific recommendations for appropriate intervention. This strategy represented an important innovation at the time, and it paved the way for subsequent discoveries of preventable environmentally-induced diseases and dysfunctions. Although today's researchers rely on highly advanced tools, such as exposure biomarkers, job-exposure matrices, and molecular epidemiology, they can still benefit from Ramazzini's teachings.

An oft-cited example of Ramazzini's writings on occupational medicine refers to mercury poisoning in mirror-makers (Fig. 1). The Magister from Carpi vividly described their miserable fate: "…these workers glower at the reflection of their suffering in the very mirrors they have made with their own hands and curse the profession they have had to follow" (1). I shall now examine how Ramazzini's research strategy has informed modern studies of mercury toxicology – how evidence was informed by learning from victims and inspired prudent action.

Figure 1. A contemporary engraving shows a mirror-maker, who – to paraphrase Bernardino Ramazzini – turns his head away from the reflection of his own suffering in the very mirror he has made, cursing the profession he had to follow (Der Spiegler, by Christoph Weigel, 1698).

Mercury rising

Mercury first became known as an environmental neurotoxicant following outbreaks of methylmercury poisoning, the most serious one happening in Minamata, Japan, during the 1950s and early 1960s, when people ate fish polluted by methylmercury from a chemical plant (6). A subsequent incident occurred during a famine in Iraq in 1971-1972, where people ate bread made from seed grain that had been treated with a methylmercury fungicide (7). Soon, the World Health Organization established an exposure limit for methylmercury based on evidence on toxicity to the adult nervous system, although the experts conceded that "the fetus may be more susceptible to methylmercury toxicity than the adult" (8).

The United Nations First Conference on the Human Environment happened in Stockholm in 1972 and effectively put the environment on the international agenda. It also resulted in the creation of the United Nations Environment Programme. Victims of industrial pollution held demonstrations to raise attention to the human health costs due to chemical pollution. As part of a group of Minamata victims, a teenager named Shinobu Sakamoto had traveled with her mother to Stockholm, and I saw her in the Danish TV news. I was in medical school in Copenhagen at the time, and my older brother was in Stockholm as the press secretary of the Danish minister of the environment, the very first in the world. This girl with spastic paresis was holding a banner protesting environmental pollution. She made a lasting impression on me; I was shocked that environmental chemicals could have such severe adverse effects, something that medical school had not prepared me for.

When looking into the evidence available at the time, I noted that the fetus was particularly vulnerable to this neurotoxicant, as expressed by a Japanese clinician: "in every case the mother was healthy, and it was not until more than three months after birth that the symptoms were recognized" (9). Further, the neuropathology findings were instructive (10). Adults dying from the disease suffered uniquely localized lesions in specific areas of the brain. Methylmercury poisoning in children and adolescents showed more widely distributed brain damage. The most severe and diffuse pattern of damage was seen in infants and children who had been poisoned prenatally (from the mother's diet). They had serious disruption of normal brain structures. These findings agreed with the clinical picture that was rather specific in adults (sensory disturbances and motor dysfunction) and more generalized in the children (6).

The reports from the poisoning cases raised some important questions: 1) Can methylmercury also cause damage to the developing brain at low doses? 2) Can toxic exposures occur from general environmental exposures far from the emission sources? 3) Is the global

environment mainly polluted from industrial sources? 4) Is developmental neurotoxicity a general concern beyond a few documented toxicants, including lead and ethanol?

Seeking answers

The key to finding answers to such questions must rely on environmental epidemiology studies that extract information from populations with exposures that cover a wide interval. I chose to collaborate with Dr. Pal Weihe and his colleagues in the Faroe Islands, a Nordic nation with a fairly homogeneous population that relies on seafood. Importantly, traditional Faroese diets include the meat of the pilot whale, a toothed whale that accumulates methylmercury from ocean food chains (11).

In 1986, we began to recruit a cohort of 1,000 births, where we obtained information from the mother and a cord blood sample for mercury analysis (12). We then waited until the children had reached school age, so that we could administer neuropsychological tests that could ascertain subtle cognitive dysfunctions. Our findings showed that, for each doubling of the prenatal methylmercury exposure, the child at age 7 had lost 1-2 months of development, corresponding to an average effect of about 1.5 IQ points (13). We complemented these tests with brain stem auditory evoked potentials that showed that the speed of transmission of electrical signals in the brain were lower at higher exposure levels (14). Most recently, we used modern imaging methods, which revealed that highly exposed children activated brain regions not needed by controls when completing simple tasks (15). Most recently, we have shown that mercury-associated deficits remain in cohort members at age 22 years (16). Thus, environmental pollution with mercury was indeed a hazard that could affect brain development in humans, and the effects were found to be lasting.

Overall, the studies inspired by poisoning victims uncovered important new information. However, the path to recognition was not without setbacks. Our first major manuscript was rejected by three journals that we first approached. When finally considered by Neurotoxicology and Teratology, major revision was requested several times (13). Right after its publication, the article was criticized in Science (17). We wondered how our article had been leaked so that a response could be written up in time for it to be published a few weeks after our journal paper was released. That was not a simple feat in 1997, but there was a clue. The Science commentary referred to our article as starting on page 1, while the printed version began on page 417. This suggests that the authors had gained access to the proof version of our article, where the pagination by default started with page 1. How the proofs made it to outside colleagues was not clear to us. Nonetheless, with close to 900 citations by now, our article is by far the most highly cited article from this specialty journal since its inception in 1987.

We soon realized that adverse health risks could be easily underestimated, rather than the opposite. First of all, in observational studies, the exposure assessment is always imprecise, thus tending to cause bias toward the null (18). This bias could be worsened by adjustment for covariates with better precision (19). As seafood nutrients could counteract some of the adverse effects, negative confounding could ensue, which would need proper adjustment to reveal the full extent of the methylmercury toxicity (20). Methylmercury easily passes the placenta, and cord blood contains about 50% higher concentrations than maternal blood, but confusion of these measurements led to underestimation of the dose dependence (21). As the brain continues to develop, early outcome assessments may be less sensitive than the assessments that become possible at school age (22). A final issue of concern is that epidemiological studies examine average effects and usually ignore individual vulnerability, e.g., due to genetic predisposition (23). All of these factors affected the recognition of methylmercury as a serious public health hazard and part of the "silent pandemic" caused by developmental neurotoxicity (24).

Given that mercury from seafood could have toxic effects, the question emerged whether the mercury from food chains originated from natural sources, such as weathering and volcanic eruptions, or from industrial releases. This consideration could not be resolved by epidemiological studies, and one approach instead focused on the exposure of polar bears, as ascertained by hair analysis. Using bear hair from the Qilakitsoq

interment in Greenland (about 1300 A.D.) as a basis, the total enrichment of mercury in the environment since preindustrial times was found to be approximately 10-fold (25), a number that agrees with model calculations (26). Thus, the environmental methylmercury exposures that cause adverse human health effects are predominantly due to man-made pollution.

Academic skepticism and vested interests

As already noted, our first report on mercury effects in Faroese children (13) was met with skepticism. The year after the article was published, the White House requested that international experts be called together to review the current evidence that methylmercury exposure from seafood might damage brain development. As a principal investigator of the Faroes study, I was invited to present at the workshop, but the organizers wanted to avoid any controversy and therefore prohibited me from interacting with the committee members and also from commenting on their findings. In its conclusions, the distinguished committee recognized "some concern that risks of lower exposure to methylmercury may exist… but there are inadequate data on this to draw meaningful conclusions at this time" (27). Although such conclusions are common when highly specialized scientists review and criticize current evidence, the lack of dialogue and the resulting impasse were unfortunate.

Following this misdirected effort, the U.S. National Research Council was asked to conduct a thorough review of the evidence, where my colleagues and I were asked to contribute clarifications and supplementary tables. The detailed report was released in 2000 and concluded that the U.S. Environmental Protection Agency (EPA) should base its exposure limit for methylmercury on the Faroes study (28). Although the EPA limit is low on an international scale, more recent data and calculations of benchmark dose results (29-31) suggest that the limit is not as protective as it should be. However, it has remained unchanged for 15 years.

One of the reasons that current evidence is not translated into prevention and public policy is that scientists generally refrain from making blunt statements, as they may inspire accusations of bias. Scientific publications traditionally contain hedged language, including such words as maybe, perhaps, and possibly, and they highlight weaknesses, caveats, and reservations. The reason for this "soft" language is that observational studies can never for certain exclude some unmeasured interference or confounder that may have blurred or biased the results (32). Even when such error is unlikely, the biomedical tradition is to downplay and avoid exaggeration (33) – despite the likely underestimation of risk referred to above. Thus, when research has potential societal or economic implications, any resulting controversies can lead to exaggerated hedging in research reports, where scientists refrain from taking sides. However, at the same time, they pave the way for claims that no proof exists of any risk. A medical researcher expressed his skepticism to a Nature writer in the following way: "Some people are convinced that mercury causes these effects and others are not so confident" (34). The same colleague noted that the Faroes population received a substantial amount of its mercury exposure from whale meat and emphasized that few people in the United States eat whale meat (35).

Mercury therefore offers an unfortunate example of how misplaced scientific skepticism may act counter to the interests of public health. Vested interests will cherish any reservations regarding research that they consider unwelcome. Their views have been vividly expressed in statements such as: "In the United States, even the most rabid environmentalist cannot point to one sickened child or doddering old fool made ill from mercury" (36). As public awareness of mercury pollution increased, the tuna industry funded a campaign for $25 million (37), with whole-page advertisements and websites with names such as "FishScam" and "MercuryFacts" (now defunct), where academic researchers and EPA representatives were ridiculed.

One of the predictable outcomes of the controversy on environmental mercury is that more research has been carried out to replicate, supplement, or explore possible caveats or reservations. This positive feedback mechanism has helped propel methylmercury to a top-priority pollutant in research. Since the introduction of the Medical Subject Heading term "methyl mercury compounds" in 1980, the National

Library of Medicine has recorded close to 5,000 articles in scientific journals on this topic, most of them from recent years. This domino effect has been dubbed the "Matthew effect" (from the gospel expression "for unto every one that hath shall be given") (38). In other words, as researchers expressed concerns about uncertainties and refrained from drawing firm conclusions, the desire to resolve the questions resulted in one of the best known environmental chemicals becoming a continuing research priority, at the expense of other poorly explored hazards.

Learning from the victims

Perhaps the research strategy and the interpretation would have been different, had we paid more attention to the problems faced by subjects and populations that were exposed to toxic amounts of methylmercury (Fig. 2). My mentor at Mount Sinai Hospital in the late 1970s, Professor Irving J. Selikoff, first President of the Collegium Ramazzini, famously said: "Never forget that the numbers in your tables represent human destinies, although the tears have been wiped away." Like Bernardino Ramazzini, Selikoff emphasized the need to learn from the victims as a primary source of information. However, during past centuries, the road was rather bumpy, and mercury-poisoned patients had to withstand a variety of medical procedures, that is, if they survived.

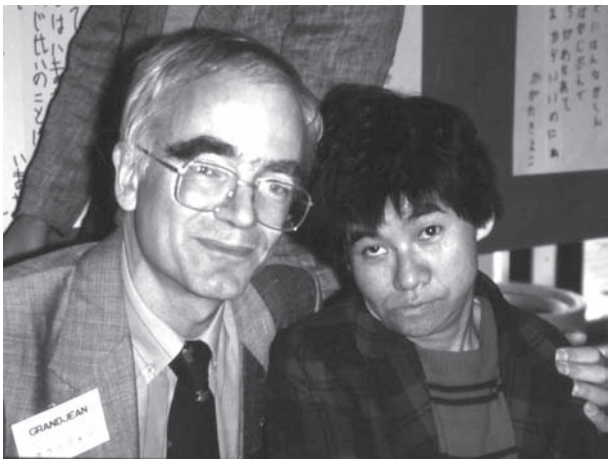


Figure 2. At a conference organized by the United Nations University in Minamata, Japan, in 1992, I first met Shinobu Sakamoto, a victim of congenital methylmercury poisoning, who 20 years earlier had traveled to Stockholm, Sweden, to participate in demonstrations in connection with the first UN conference on the environment.

Mercury compounds were applied for centuries as pharmaceuticals, especially to treat syphilis. Even the first recorded case of methylmercury poisoning in 1865 was paradoxically treated with mercury. Thus, a laboratory technician who had tried to synthesize the substance was hospitalized, as he was unable to stand without support, suffered speech problems, impairment of sight and hearing, and had numbness of his hands. These symptoms were similar to those that much later beset the residents of Minamata. As standard treatment did not work, the physician decided to add a pharmaceutical commonly used at the time – calomel (mercury chloride). That of course did not help either, and the patient soon expired (39).

Diagnosis could be problematic at a time when blood-mercury analysis was not easily available. One occupational medicine specialist called exposed workers "hysterical" (40), possibly due to symptoms of neurotoxicity, and another doctor treated a worker with electroshock therapy (which again did not help) (41).

Perhaps the major suffering happened in Minatama and the surrounding area in Japan, where the cause of the mysterious disease was disputed for years (6). Recognition of the factory effluents as the source of the pollution was delayed by company representatives, who insisted that mercury releases from the factory could not have played any role (6). As a result, the toxic exposures continued.

Serious human misery happened during the famine in Iraqi where thousands of victims were poisoned by mercury-tainted grain (7). Most of the patients were from Kurdistan, perhaps not a complete accident during the rule of then-President Saddam Hussein. Unfortunately, the data that were shared with Western researchers were controlled by a single doctor, who turned out to be the dictator's personal physician (42). Methylmercury was widely used as a fungicide, and in Sweden this practice was banned only when mercury-contaminated chicken eggs were discovered, thus suddenly threatening agricultural exports (43).

Industrial mercury releases can cause accumulation of methylmercury downstream (44), as was first

documented in Canada. The Ojibway tribes knew that they were exposed to some *pijibowin* poison (45) and challenged the government to rectify the situation. In the end, a compensation of $8,000 was paid to each resident on the affected reserves, and those with methylmercury poisoning acknowledged by a disability board received a small amount every month. The mercury pollution remains, though.

Now that we are recognizing the danger from environmental mercury exposure, and UN member states have recently approved the Minamata Convention (46), a sad paradox has become apparent (47). Mercury in the environment will persist for many decades, and seafood contamination will not diminish for many, many years (48). So the victims of today are global.

Widening perspectives

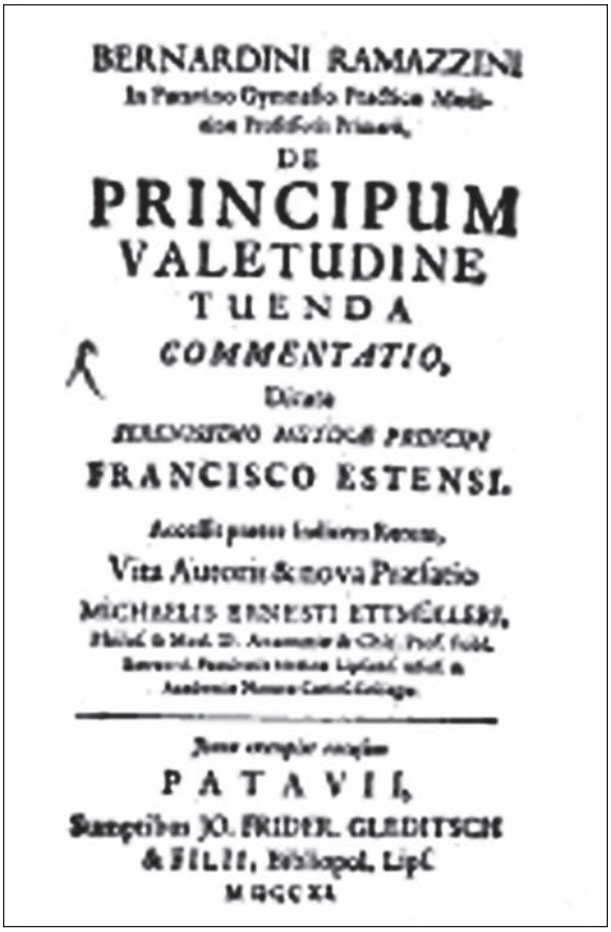
The evidence on methylmercury and lead (24) as well as the discovery of the fetal alcohol syndrome (49) suggested that toxicity to brain development might not represent a target-organ effect specific to a small number of toxic chemicals. On the contrary, brain development is an extremely intricate process that is particularly complicated in humans due to the superior nervous system functions (50). Vulnerability to toxic effects can therefore be looked upon as a price we pay for the development of our sophisticated brains. Still, at this point, proper documentation on developmental neurotoxicity is available only on a small number of substances. In these cases, developmental exposures were assessed, e.g., from chemical analyses of blood and urine samples from the mother or blood from the umbilical cord. As sensitive tests of brain functions are usually not feasible until school age when the major domains have sufficiently matured, prospective studies need to cover a time period that can easily last seven or eight years. Given such requirements to obtain proper documentation, it is understandable that science has addressed only a few neurotoxicants so far. In contrast, neurotoxicity in adults is usually documented from occupational exposures, accidental intakes or the like, where an obvious connection between the chemical causation and the neurological outcomes can be observed.

So far, convincing evidence is available only on 12 substances (including methylmercury, lead, and ethanol) that can now be labeled as human developmental neurotoxicants (24), half of them having been documented only in recent years. In contrast, 214 industrial chemicals are known to be neurotoxic to adults. Given the severe difficulties in obtaining detailed evidence on developmental brain damage, a prudent conclusion is that all of those 214 substances should be considered hazards to human brain development at doses that might very well be much, much lower than those causing toxicity – perhaps even reversible – to mature brains (24).

This notion fits in well with an emerging paradigm called Developmental Origin of Health and Disease (DOHaD) (51, 52). Although at first mainly thought to comprise nutrients, energy intake, tobacco smoke, and pharmaceuticals (53), this concept fits at least as well with the evidence accumulated on developmental toxicants (51) that are now causing what has been labelled a "silent pandemic" (50, 54). This insight therefore suggests that early development is the most important time for prevention of non-communicable disease. As expressed by the World Health Organization in the recently approved Minsk Declaration: "Action must therefore focus on pre-conception, pregnancy, fetal development and on the most vulnerable life stages" (55).

Ramazzini's perspective

After completion of his textbook in occupational medicine, the Magister from Carpi published a book that is less widely known, entitled "De Principum Valetudine Tuenda Commentatio" (Fig. 3). The author explained the purpose of this publication: "The public well-being depends wholly of the health of princes; it follows from this that nothing must be left untried to safeguard it." To appreciate why the father of occupational medicine might wish to write a whole book on how to keep the Duke of Modena (the "Prince") healthy, one must consider the dramatic history that involved abduction of the Duke by a foreign nation and the adverse effects of the unrest. So the health of the ruler was indeed a concern that had to be shared by Ramazzini and his fellow citizens.


BERNARDINI RAMAZZINI

DE

PRINCIPUM

VALETUDINE

TUENDA

COMMENTATIO,

FRANCISCO ESTENSI.

Vita Autoris & nova Præfatio

PATAVII,

M DCC XI

Figure 3. Bernardino Ramazzini published his last book in 1712 where he outlined the efforts needed to maintain the best possible health for the Duke of Modena. While this dedication to the ruler was understandable at the time, Ramazzini would have turned his attention elsewhere, had he been around today.

But how would Ramazzini have responded to the threats to human health of today – would he still have provided recommendations on how to promote the health of the powers that be? Although we owe much to the mayor of Carpi, Alberto Bellelli, and wish him a healthy and successful life, I know that the Mayor considers himself much less powerful than the Duke of Modena at Ramazzini's time. At the present time where rulers are less powerful, and where Italian prime ministers change quite frequently, Ramazzini would rather have focused on the future and the health of generations to come. I would think that the evidence on developmental toxicity from mercury and other neurotoxicants and the DOHaD paradigm would have impressed him. A proper title of a new book might therefore be "De Posterorum Valetudine Tuenda Commentatio", i.e., emphasizing the health of our successors, though of course Ramazzini would have chosen another language than Latin to highlight the health of the next generation. Sadly, we can't count on any help in this regard from the Great Magister, but at least his teachings will hopefully continue to provide inspiration for years to come.

References

1. Ramazzini B. De morbis artificum Bernardini Ramazzini diatriba. Diseases of workers. The Latin text of 1713 revised (translated by Wright WC). Chicago, Ill: The University of Chicago press, 1940.
2. Franco G. Ramazzini's «De morbis artificum Diatriba» and society, culture, and the human condition in the seventeenth century. Int J Occup Environ Health 2000; 6: 80-5.
3. Gochfeld M. Chronologic history of occupational medicine. J Occup Environ Med 2005; 47: 96-114.
4. Franco G. Ramazzini and workers' health. Lancet 1999; 354: 858-61.
5. Franco G. A pioneer of public health, Bernardino Ramazzini. Ann Ig 2013; 25: 273-80.
6. Harada M. Minamata Disease (translated by Sachie Y, George TS). Tokyo: Iwanami Shoten, 2004.
7. Bakir F, Damluji SF, Amin-Zaki L, *et al.* Methylmercury poisoning in Iraq. Science 1973; 181: 230-41.
8. JECFA. Evaluation of certain food additives and contaminants (Twenty-second report of the Joint FAO/WHO Expert Committee on Food Additives). Geneva: World Health Organization, 1978
9. Kitamura S, Miyata C, Tomita M, *et al.* Epidemiological investigation of the unknown central nervous disorder in the Minamata district. Kumamoto Med J 1957; 31 (Suppl. 1): 1-9.
10. Takeuchi T, Eto K. The pathology of Minamata Disease. A Tragic Story of Water Pollution. Fukuoka: Kyushu University Press, 1999.
11. Julshamn K, Andersen A, Ringdal O, *et al.* Trace elements intake in the Faroe Islands. I. Element levels in edible parts of pilot whales (Globicephalus meleanus). Sci Total Environ 1987; 65: 53-62.
12. Grandjean P, Weihe P, Jørgensen PJ, *et al.* Impact of maternal seafood diet on fetal exposure to mercury, selenium, and lead. Arch Environ Health 1992; 47: 185-95.
13. Grandjean P, Weihe P, White RF, *et al.* Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol 1997; 19: 417-28.
14. Murata K, Weihe P, Budtz-Jørgensen E, *et al.* Delayed

brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury. J Pediatr 2004; 144: 177-83.
15. White RF, Palumbo CL, Yurgelun-Todd DA, *et al.* Functional MRI approach to developmental methylmercury and polychlorinated biphenyl neurotoxicity. Neurotoxicology 2011; 32: 975-80.
16. Debes F, Weihe P, Grandjean P. Cognitive deficits at age 22 years associated with prenatal exposure to methylmercury. Cortex 2016; 74: 358-69.
17. Egeland GM, Middaugh JP. Balancing fish consumption benefits with mercury exposure. Science 1997; 278: 1904-5.
18. Grandjean P, Budtz-Jørgensen E. An ignored risk factor in toxicology: The total imprecision of exposure assessment. Pure Appl Chem 2010; 82: 383-91.
19. Budtz-Jørgensen E, Keiding N, Grandjean P, *et al.* Consequences of exposure measurement error for confounder identification in environmental epidemiology. Stat Med 2003; 22: 3089-100.
20. Budtz-Jørgensen E, Grandjean P, Weihe P. Separation of risks and benefits of seafood intake. Environ Health Perspect 2007; 115: 323-7.
21. Mahaffey KR, Clickner RP, Bodurow CC. Blood organic mercury and dietary mercury intake: National Health and Nutrition Examination Survey, 1999 and 2000. Environ Health Perspect 2004; 112: 562-70.
22. Rohlman DS, Anger WK, Tamulinas A, *et al.* Development of a neurobehavioral battery for children exposed to neurotoxic chemicals. Neurotoxicology 2001; 22: 657-65.
23. Julvez J, Grandjean P. Genetic susceptibility to methylmercury developmental neurotoxicity matters. Front Genet 2013; 4.
24. Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. Lancet Neurol 2014; 13: 330-8.
25. Dietz R, Riget F, Born EW, *et al.* Trends in mercury in hair of Greenlandic polar bears (Ursus maritimus) during 1892-2001. Environ Sci Technol 2006; 40: 1120-5.
26. Fisher JA, Jacob DJ, Sørensen AL, *et al.* Factors driving mercury variability in the Arctic atmosphere and ocean over the past 30 years. Global Biogeochem Cycles 2013; 27: 1226-35.
27. NIEHS, editor Workshop organized by Committee on Environmental and Natural Resources (CENR), Office of Science and Technology Policy (OSTP), The White House Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury; 1998 November 18-20, 1998.
28. National Research Council (U.S.). Committee on the Toxicological Effects of Methylmercury. Toxicological effects of methylmercury. Washington, DC: National Academy Press; 2000.
29. Grandjean P, Budtz-Jørgensen E. Total imprecision of exposure biomarkers: implications for calculating exposure limits. Am J Ind Med 2007; 50: 712-9.
30. Oken E, Wright RO, Kleinman KP, *et al.* Maternal fish consumption, hair mercury, and infant cognition in a U.S. Cohort. Environ Health Perspect 2005; 113: 1376-80.
31. Lederman SA, Jones RL, Caldwell KL, *et al.* Relation between cord blood mercury levels and early child development in a World Trade Center cohort. Environ Health Perspect 2008; 116: 1085-91.
32. Hyland K. Hedging in Scientific Research Articles. Amsterdam, The Netherlands: John Benjamins; 1998.
33. Grandjean P. Seven deadly sins of environmental epidemiology and the virtues of precaution. Epidemiology 2008; 19: 158-62.
34. Pearson H. Mercury affects brains of adolescents. Nature, February 6, 2004
35. Gorman J. Does Mercury Matter? Experts Debate the Big Fish Question. New York Times, July 29, 2003.
36. Bailey E. Mines' Toxic Legacy of Mercury Still Haunts State. Los Angeles Times, October 31, 1999.
37. Rodgers T. As canned tuna sales dive, companies plan ad blitz to reel buyers back in. The San Diego Union-Tribune, July 27, 2005.
38. Grandjean P, Eriksen ML, Ellegaard O, *et al.* The Matthew effect in environmental science publication: a bibliometric analysis of chemical substances in journal articles. Environ Health 2011; 10: 96.
39. Edwards GN. Two cases of poisoning by mercuric methide. Saint Bartholomew's Hospital Reports 1865; 1: 141-50.
40. Höök O, Lundgren KD, Swensson Å. On alkyl mercury poisoning; with a description of two cases. Acta Med Scand 1954; 150: 131-7.
41. Herner T. Poisoning from organic compounds of mercury [in Swedish] Nordisk Medicin 1945; 26: 833-6.
42. Hightower JM. Diagnosis mercury: money, politics, and poison. Washington, DC: Island Press/Shearwater Books; 2009.
43. Tejning S, Vesterberg R. Alkyl mercury-treated seed in food grain. Poultry Sci 1964; 43: 6-11.
44. United Nations Environmental Programme (UNEP). Global Mercury Assessment Geneva: UNEP Chemicals, 2002.
45. Erikson K. A new species of trouble. New York: Norton & Co.; 1994.
46. Bank MS, Vignati DA, Vigon B. United Nations Environment Programme's Global Mercury Partnership: science for successful implementation of the Minamata Convention. Environ Toxicol Chem 2014; 33: 1199-201.
47. Bender M, Lymberidi-Settimo E, Groth III E. New mercury treaty exposes health risks. J Public Health Policy 2014; 35: 1-13.
48. Mason RP, Choi AL, Fitzgerald WF, *et al.* Mercury biogeochemical cycling in the ocean and policy implications. Environ Res 2012; 119: 101-17.
49. Lemoine P. Outcome of children of alcoholic mothers (study of 105 cases followed to adult age) and various prophylactic findings. Ann Pediatr (Paris) 1992; 39: 226-35.
50. Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. Lancet 2006; 368: 2167-78.
51. Grandjean P, Bellinger D, Bergman A, *et al.* The Faroes statement: human health effects of developmental exposure to chemicals in our environment. Basic Clin Pharmacol Toxicol 2008; 102: 73-5.

52. Barouki R, Gluckman PD, Grandjean P, *et al.* Developmental origins of non-communicable disease: implications for research and public health. Environ Health 2012; 11: 42.
53. Barker DJ. The origins of the developmental origins theory. J Intern Med 2007; 261: 412-7.
54. Grandjean P. Only One Chance. New York: Oxford University Press, 2013.
55. World Health Organization. The Minsk Declaration: The Life-course Approach in the Context of Health 2020. Copenhagen: World Health Organization, Regional Office for Europe, 2015.

Received: 13.10.2015
Accepted: 4.1.2016
Address: Dr. Philippe Grandjean
Environmental Medicine,
J.B.Winslowsvej 17A, 5000 Odense, Denmark
Tel. +4565503769
Fax +4565911458
E-mail to: pgrand@sdu.dk