Importance of the Great Lakes

The article by Knap et al., "Indicators of Ocean Health and Human Health: Developing a Research and Monitoring Framework" (Knap et al. 2002), was a welcome overview of issues that link the environmental condition of marine/ocean ecosystems and human disease. The complement to the growing concern about the connection between health and the marine environment is a corresponding emphasis on large freshwater lake ecosystems and human health.

In the United States and Canada, for example, the Great Lakes basin contains a set of inland seas that are oceanographic in scale. They serve as a highway for international maritime commerce and support a $1 billion/year recreational and commercial fishing industry. In addition, they must also supply drinking water for over 15 million people.

The Great Lakes hold about 20% of the world's surface freshwater. In this context, the degradation of the Great Lakes ecosystem through chemical and biological contamination presents an enormous challenge for the future. Questions about the impact of methyl mercury, polychlorinated biphenyls, and other chemicals on the health of those who eat fish from the Great Lakes; about the role of bacterial loading of coastline beaches on disease; and about the quality of drinking water taken from the lakes are among those in need of intense study.

Surprisingly, in comparison with the number of research organizations and funding opportunities that concentrate on the marine environment, there are very few governmental or academic programs that target the Great Lakes environment. In this context, it should be a priority to develop research programs that can enlarge the knowledge base so that the Great Lakes can be sustained as the centerpiece of our freshwater resources.

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Appreciation for "Remembering Alice Stewart"

EHP deserves appreciation for publishing "Remembering Alice Stewart" (Mead 2002). However, I would like to address a few inaccuracies and important omissions about this scientist's contributions that warrant comment.

The Oxford Survey of Childhood Cancers (OSCC) did not limit itself to "children [who] had died of lymphatic leukemia," (Mead 2002) but it included all children who had died of any form of cancer, anywhere in the United Kingdom. Mead's statement that Stewart found

> that children who died of cancer had received prenatal X-rays twice as often as healthy children

should read that

> among the children that had died of cancer, twice as many had been exposed to prenatal X-rays, as compared to the group of healthy children serving as controls.

Mead correctly stated Stewart's conclusion that

> radiation protection committees… had grossly underestimated the [unavoidable] number of cancers due to background radiation,

but failed to refer to her pivotal study linking variations in local background exposure levels over a narrow grid all across the British Isles with variations in local childhood cancer (Knox et al. 1988). This observation led Stewart to infer that while about 7% of all childhood cancers for 1950–1980 were associated with prenatal X-rays (declining thereafter with declining doses), more than 70% were associated with unavoidable *in utero* exposures to natural background radiation (Knox et al. 1988). This study contradicted the popular contention that small anthropogenic increases in population exposures from radioactive fallout or environmental contamination have no detectable detrimental health consequences.

Based on her findings, Stewart developed a model of cancerogenesis that links a strongly age-dependent risk for radiation-induced cancer (highest during early fetal development, lower by at least a factor of three before birth, lowest in young adults, then rising again sharply after 40 years of age) with an age- and general health-dependent variation in individual immune defense competence. The evidence for this relation combines the findings of the OSCC with those of nuclear workers studies.

Mead's article (2002) and other reports have focused primarily on the politically explosive challenges that Stewart's work presented to official radiation risk assessments. However, for the history of pioneering scientific ideas it is far more significant to note that most of these contradictions derive from Stewart's unconventional insights into the confounding effects of selection (such as healthy worker and healthy survivor effect) and of competition between malignant and nonmalignant causes of deaths on epidemiologic mortality studies. Ignoring these factors have led to dramatically different outcomes in the analysis of the same statistical database.

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Nitrate and Methemoglobinemia

After they had collected extensive particulars in the Transylvania Region of Romania for an epidemiologic cohort study exploring a hypothetical relationship between high nitrate infant exposure and later neuropsychologic development, Zeman et al. (2002) tried to take advantage of these data in order to settle the question of whether infant methemoglobinemia is correlated with mean daily nitrate intakes or with diarrheal disease in the first months of life. However, we have serious reservations about their paper, especially their methodology.

In the study, proxy interviews of primary caregivers were used to reconstruct mean daily dietary nitrate exposures, but these interviews took place nearly 5 years after the clinical events. Although such data may be accurate enough for the study of a chronic disease, their reliability and accuracy are questionable in the study of an acute condition such as methemoglobinemia.

Well-water samplings were intended to evaluate water nitrate levels and reconstruct mean daily dietary nitrate exposures; they too were taken nearly 5 years after the clinical incidents. Nitrate levels in well water vary with time and season, which again opens the method to criticism.

Infant methemoglobinemia is an acute event. Usually the only clinical symptom (i.e., cyanosis) spontaneously disappears in several minutes, at the most in a few hours. We wonder what good it serves to try to correlate such an acute and transitory infant

disease with mean daily nitrate intake during the first months of life. Moreover, why did interviewers (Zeman et al. 2002) ask primary caregivers to recall dietary habits of the child at both 2 and 6 months of life, when all clinical incidents regarded as methemoglobinemias appeared before (in their Table 1) or around (noted in text) 2 months of life?

Our primary criticism of the paper (Zeman et al. 2002) refers to the recruitment criteria of the infant methemoglobinemia cases: in all the cases, diagnoses are merely clinical. It is commonly known that cyanosis appears when methemoglobin levels exceed 10% (not 3% as might by construed from the comments of the authors). Of course, methemoglobinemia is not the only cause of infant cyanosis. Other pathologic conditions are quite possible. The only way to diagnose a case of infant methemoglobinemia with assurance is to measure the methemoglobin level in the blood at the time of the clinical incident. The physician will be justified in recognizing the case as infant methemoglobinemia if, and only if, the methemoglobin level exceeds 10%.

These important reservations having been stated, it is not at all surprising that Zeman et al. (2002) found the strongest association with estimated nitrate exposure, given that the infants were exposed to extremely high nitrate levels. The mean nitrate content of the drinking water in the cases was estimated at over 25 times the current U.S. drinking water maximum contaminant level (MCL) of 10 ppm nitrate nitrogen (U.S. Environmental Protection Agency 1991). In all of the cases, the nitrate content of the drinking water was at least 5 times higher than the MCL, and one case was 120 times the U.S. official limit.

Despite these extreme water nitrate concentrations, it is possible to note, as Zeman et al. (2002) did, that at lower estimated nitrate exposures diarrhea seems to be able to favor the appearance of infant methemoglobinemia. We are not sure that their work really succeeds in demonstrating such a link, but a number of papers published in the last few years [cited by Avery (1999) and L'hirondel and L'hirondel (2001)] had already convinced us of it.

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Methemoglobinemia Risk Factors: Response to Avery and L'hirondel

Doing and discovery are always harder than critique. Should one have the opportunity, or misfortune, of merely reviewing the fieldwork of others, one would have the luxury of never being criticized. Real world, field epidemiology does not provide that luxury.

In the real world of epidemiology, where individuals apply shoe leather to pavement—or to the village farmer's field, as the case may be—answers are carefully pried from conditions as they exist; there is nothing as tidy as a controlled laboratory setting.

Despite the best efforts, case–control studies are always open to criticisms and specific weaknesses. Case–control studies are subject to recall bias; they are subject to difficulties in classification of cases and controls; you cannot calculate incidence rates from this study design; and causality can be difficult to establish (which Avery and L'hirondel failed to point out) (Gordis 2000).

What do field researchers do under such conditions? They use as many sources of information as possible to assure that internal validity of study design is the best that it can be, given the circumstances in which diseased individuals are found. Careful design included several safeguards.

First, when methemoglobin levels were not available on medical charts, multiple criteria for the determination of a case were used (Zeman et al. 2002a), including exposure history and positive ascorbic acid response to dyspneic respiratory distress. We are well aware that a clinical case of methemoglobinemia does not manifest at 3% methemoglobin in the blood and are not at all sure how that was "construed" from the text.

Second, we accessed recall bias in reported feeding regimes by comparing reports from cases and controls of amount and frequency of feeding; we found no significant differences between the groups using analysis of variance (Zeman et al. 2002a). Although we must always assume that some recall bias operates in the case of dietary recall, research has indicated that surrogate interviews are most accurate when the surrogate recalls information from salient periods of a dependents life, such as the first 6 months (Baranowski 1991; Livingstone 1992). Further, it is important to focus on windows of exposure for the sake of recall and to clearly define exposure, another concern of the case–control study design. In this case, we used both the needs of a larger cohort study and a nested case–control study to choose windows of exposure (Zeman et al. 2002a), which is entirely defensible on the grounds that the majority of methemoglobinemia cases occur in the first 6 months of life. These allowed us to capture the majority of methemoglobinemia cases and, in many instances, to see how exposures changed over time. Additional methodologic reviews are cited in our article (Zeman et al. 2002b).

We correlated levels of analyzed nitrate/nitrite in well water with Sanitary Police Records made following methemoglobinemia incidents (Zeman et al. 2002a). In all cases and controls, the water source for the child had to be the same source implicated in the original incident. The average age of wells included in this study was 38.6 years, ranging from 6 years to an estimated > 100 years of continuous use. Further, the use of nitrogen-containing fertilizers has decreased since the early 1990s, and compost-based applications have gone up because of economic conditions. All current measured levels were taken in the spring of the year, the same time that the majority of methemoglobinemia cases occurred (Zeman et al. 2002a).

All epidemiologic studies are subject to weaknesses, but the determinates of causality include strength of association, biological mechanism, time series of events, dose–response relationships, and consistency of findings (Greenberg et al. 1996). It is in these basic tenets of the practice of epidemiology in which we find the reasons, justification, and value of this work.

Any case–control study can be improved through the use of a prospective study design; but is that ethical, given the extremely high levels of exposure that exist in these rural communities? We prefer to focus additional work on finding ways to alleviate these exposures, and we wonder why more non-governmental organizations are not working to do the same, rather than to befuddle the practice of public health and roll back maximum contaminant levels for known environmental toxins.

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Addressing Global Warming

The issue of global warming is one that reaches beyond the question of whether the atmosphere is indeed heating up due to the long enduring emission rates of greenhouse gases. Although debate may continue regarding whether global warming is real or not, another issue worth examining is whether democratic systems of government are effective in protecting society's welfare against systematic long-enduring threats such as global warming.

Democracy appears to harness a collective intelligence of a population for the purpose of protecting the population's welfare. Candidates for political office are elected on the basis of how well they represent the views and interests of the populace.

But just what are the interests of the populace? Is society's long enduring survival interests always aligned with the collective interests of a given population?

In the early stages of global warming, when there is no imminent threat to the population—regardless of the threat to future generations—a given populace cannot be expected to democratically elect leadership who will force the population to responsibly address the global warming issue. The single lifetime interests of citizens in the population will not be sufficiently aligned with the multiple lifetime interests of the society they live in.

The global warming issue needs to be addressed strongly in its early stages in order to safeguard life on our planet from threat of future extinction. For this reason, it appears to me that democracy may be an inadequate means of governing all issues relevant to a society's welfare in the 21st century.

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Estimating Costs of Environmental Disease

Due to effective control programs in the industrialized world, childhood mortality from infectious diseases has decreased dramatically over the past 140 years (DiLiberti and Jackson 1999). In recent years, increased attention has focused on chronic childhood diseases such as asthma and certain neurodevelopmental disorders. Although the etiology of these diseases is complex, there is substantial evidence linking the environment to the onset or exacerbation of certain chronic conditions.

Although such relationships have been proposed, significant uncertainties remain, and more research is needed to assess and quantify the impact that environmental chemicals have on children's health. Landrigan et al. (2002) estimated a total cost to society of $54.9 billion (range: $48.8–$64.8 billion) per year resulting from disease associated with the exposure of children to environmental chemicals. Although such an exercise can be valuable for setting public health priorities, quantification of cost estimates may be overstating the scientific certainty of the disease–environment relationships. This leaves the methodology open to criticism and makes the results difficult to interpret.

The well-known effect of lead exposure on neurodevelopment in children provides the largest component ($43.4 billion) of the estimate produced by Landrigan et al. (2002). Meta-analysis of several data sets shows an inverse relationship between blood lead level and IQ in children (Schwarz 1994). This relationship has served as the basis for several estimates of the potential costs savings resulting from the reduction in environmental lead, as well as its impact on intelligence and health over the past 25 years (Grosse et al. 2002; Salkever 1995). Decreased lead in the environment since the 1970s has reduced the average blood lead level in children by approximately 15 μg/dL—from 17.8 μg/dL in 1970 to a current level of approximately 2.7 μg/dL (Landrigan et al. 2002). Grosse et al. (2002) have suggested that this has resulted in an increase in average IQ of almost 4 points. Landrigan et al. (2002) based their cost estimate for blood lead on the impact of making further reductions from the current blood level down to zero. Even if the linear relationship between blood lead levels and IQ points is valid below the current levels—a hypothesis that is not directly supported by any data—the average annual cost estimated by Landrigan et al. (2002) is on the high end of the range of other estimates based on the same data (e.g., Grosse et al. 2002). Although Landrigan et al. (2002) acknowledged the lack of data to support the blood lead–IQ correlation at low blood concentrations, the dollar figures they estimated contribute by far the most substantial portion to the overall cost estimate.

Landrigan et al. (2002) also estimated the costs associated with neurodevelopmental disorders, childhood cancer, and asthma caused by environmental chemicals. In this pioneering area, they estimated an environmentally attributable fraction (EAF) for each disease by convening a panel of several experts for each disease. The EAF used in the cost estimate is the mean value provided by the respondents on the panel, which we determined to be 30% for asthma, 5% for cancer, and 10% for neurobehavioral disorders such as dyslexia, attention-deficit hyperactivity disorder, autism, and intelligence reductions. Landrigan et al. (2002) estimated that environmentally related neurodevelopmental disorders cost $9 billion/year. Asthma and cancer make up the remaining $2.5 billion of the $54.9 billion estimate. There is no doubt a great deal of debate within the scientific community over what the actual EAFs may be. Some scientists may speculate that an appropriate EAF is zero, while others speculate a higher number. The "average" opinion of a small expert panel will not reflect this debate. As an example, Wallstein and Whitfield (1986) asked six experts for estimates of the amount of IQ deficit that would result in children with blood lead levels of 5 μg/dL. Three of the six experts (50%) estimated no IQ deficit. The remaining experts estimated values less than 3 IQ points. The mean estimate from all six would be just less than 1 IQ point, neglecting the fact that one-half of the experts estimated no deficit.

Landrigan et al. (2002) used the estimate of $54.9 billion/year in costs related to environmental diseases in children to argue that the expense of further research in this area is comparatively minimal. This is a laudable goal, but it may not be the best approach. The fact that there is such uncertainty in EAFs for these diseases is justification enough for further research. Cost estimates such as this must be produced and published with caution. The cost numbers presented here have been picked up by the mass media.

Because of the brevity of such presentations, details of how the estimate was obtained and the uncertainties in the methodology often cannot be made clear. The extremely high cost numbers could provide easy targets for critics. Instead of serving as a justification for more research, such estimates may cause researchers studying the health effects of environmental chemicals to lose credibility within the larger community of scientific and medical research.

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Estimated Costs of Environmental Disease: Response to Rigas

We thank Rigas for his thoughtful comments. We would be the first to agree with him that more research is needed to better define etiologic associations between pediatric disease and toxic chemicals and to further refine estimates of the costs of diseases of environmental origin in children. The field is still very much in its early stages.

That said, however, we disagree with Rigas' argument that an effort to quantify the costs of disease of environmental origin in children is not credible. We are of the opinion that this effort is, in fact, essential *a*) to counter one-sided and often ill founded claims about the high costs of controlling pollution, *b*) to examine the costs of diseases of environmental origin in relation to the costs of other societal problems, and *c*) to guide the establishment priorities for research and prevention.

In defense of our analysis (Landrigan et al. 2002), we note that the environmentally attributable fraction (EAF) methodology that we used derives directly from an Institute of Medicine report "Costs of Environment-Related Health Effects: A Plan for Continuing Study" (Institute of Medicine 1981); the committee that developed that report was chaired by Nobel Laureate economist Kenneth Arrow, who also advised our study. This methodology has been used with great success in estimating the costs of occupational disease in American workers (Fahs et al. 1989; Leigh et al. 1997), and those estimates have been relied upon extensively by the National Institute for Occupational Safety and Health (NIOSH) and by state health agencies for over a decade. We acknowledge, of course, that uncertainty surrounds any estimate of EAF and that the estimates will reflect the beliefs and the experience of the members of the consensus panel. That is why we indicated a range of uncertainty around each of our estimates, and why we populated our panels with naturally recognized subject matter experts who had no financial or other conflicts of interest in regard to the topics under evaluation.

Rigas challenges our analysis of the costs of current levels of exposure to lead (Landrigan et al. 2002) on the grounds that it has not been proven that the linear, inverse dose–response relationship that has been observed repeatedly between blood lead level and intelligence (IQ) extends downward to a blood lead level of zero. In our report we acknowledged that limitation, but we argue that the linear calculation is biologically plausible because "to date cognitive deficits have been associated with all ranges of blood lead concentration studied, and no evidence of a threshold has been found." Indeed, the most recently conducted research (Lanphear et al. 2000) found a negative association between blood lead level, reading ability, and mathematical ability at blood lead levels as low as 5 μg/dL, with no evidence of a threshold below that mark. Moreover, our conclusions on the high costs associated with present day exposures of American children to lead are buttressed by another report recently published in *Environmental Health Perspectives,* which analyzed the benefits to American society that have resulted from the removal of lead from gasoline (Grosse et al. 2002). That study found that the gain in children's intelligence that resulted from the reduction in blood lead levels following the removal of lead from gasoline has created an increase in national economic productivity, which in each annual birth cohort amounts to $213 billion.

Finally, in counterpoint to Rigas' implied criticism that our conclusions (Landrigan et al. 2002) are inflated, we note that in developing our estimates we consistently erred in the direction of conservatism. We examined only four categories of disease. We avoided consideration of disease entities for which there exist strong suspicions of environmental etiology but for which quantitative data are lacking. We chose not to estimate costs for which public data were not readily available, for example, the costs associated with the special education of children who have suffered lead poisoning. And last, we chose not to quantify the costs of pain and suffering.

Almost certainly the true annual costs of disease of environmental origin in American children are greater than our estimate of $54.9 billion. Those true costs will come to be more fully appreciated as future research elucidates additional etiologic connections between environmental exposures and pediatric illness.

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