The Canadian Association
for Children and Adults
with Learning Disabilities

L'Association canadienne
pour enfants et adultes ayant
des troubles d'apprentissage

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JAN 20 1986

January 15, 1986

Dr. John R. Rosen, M.D.,
Professor of Pediatrics
Head, Division of Pediatric Metabolism
Albert Einstein College of Medicine
111 East 210th Street
Bronx, New York, NY 10467 USA

Dear Dr. Rosen:

Today I was to attend a meeting of the Toronto Board of Health, by invitation, on the subject of lead in gasoline and the interim report of the Royal Society. I was delighted that the meeting was cancelled temporarily, as today I received a copy of your letter to Dr. Hare, and the rebuttal to that report prepared by yourself, Dr. Needleman, Dr. Schwartz, and Dr. Weiss.

A coalition of the organizations copied with this letter met with Mr. Thomas McMillan, Minister of the Environment on December 9th and made strong and joint recommendations for a speed-up of the lead phase-down program in Canada. We also indicated to him that we did not agree with the conclusions of the Royal Society report.

On behalf of the organizations represented, may I express our admiration and gratitude to all the authors of this important document. There is no doubt that your statement and letter will give our position a powerful assist here. I would support your request that it be included in the final report of the Commission to the Minister.

With much appreciation, I remain

Barbara McElgunn

Barbara McElgunn (Mrs.), Research and Liaison Officer (Health)

c.c. Dr. John Tibbles, CACLD, Professional Advisory Board
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January 3, 1986

Dr. F. Kenneth Hare
Chairman,
The Royal Society of Canada
Commission on Lead in the Environment
241 Jarvis Street
Toronto, Ontario
Canada M5B 2C3

Re: Interim Report: Lead in Gasoline, issued by the Commission on Lead in the Environment - 9/85.

Dear Dr. Hare:

Four American scientists (Drs. H. Needleman, J.F. Rosen, J. Schwartz and B. Weiss) were invited by the Society and Commission to present information in our fields of expertise at the Health Effects Workshop on Lead in Humans on March 29 and 30, 1985 in Ottawa. We were also requested to submit papers to the Commission for inclusion in its final report to the Minister. Recently, each of us received and reviewed the Commission's Interim Report cited above; and this is a joint letter from the four of us to provide you and the Commission with our collective evaluation of the report.

In general, the report ignores many important scientific findings, fails to recognize the significance of the accumulated toxicological data and adopts a policy of requiring proof of symptomatic lead toxicity in Canadian citizens, before considering the compelling priority - prevention of disease to enhance public health. Instead of protecting public health, the theme developed in the report is that the health of the public need not necessarily be protected further from lead toxicity until clinically overt disease becomes evident. Furthermore, the Commission indicates that evidence of clinically overt disease should be ignored until established beyond any reasonable doubt. For those of us who are familiar with the signs, symptoms and clinical course of lead toxicity in children and adults, the Commission's archaic position ultimately means that irreversible disease must be present before Canadian citizens may be more stringently protected from this preventable disease. The Commission should know now and forever that once children become overtly symptomatic, in the majority of cases, irreversible and severe damage to the central nervous system has already occurred.

Statements in the document that "no conclusive proof has been found" are applied to areas where substantial evidence of adverse health effects of lead has been demonstrated in humans. Statements of this type often fail to reflect concensus and accumulated judgement within the scientific community; and, even

where appropriate, such statements imply directly that convincing evidence of a clearly recognized health hazard to children must be ignored, if the evidence is not beyond "a shadow of a doubt." The Commission reveals a willingness to compromise protection of the public health, even when substantial evidence of clinically overt symptoms exists.

In summary, the Commission's report is a disservice to the health of Canadian citizens of all ages and to the cause of informed regulations to prevent this disease. The four of us, who participated in the "process," believe that our efforts were not taken seriously and that we were used to provide a similacrum of objectivity.

A collaborative rebuttal to the Commission's report is attached to this letter; and we are formally requesting herein that this letter and attached rebuttal also be included in the Commission's final report to the Minister. As the corresponding scientist for the four of us, I would appreciate an answer concerning this request.

Sincerely,

John F. Rosen, M.D.
Professor of Pediatrics
Head, Division of
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Albert Einstein College
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JFR:mh
Encl.
cc:The Hon. Thomas Mcmillan, P.C., M.P.
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Rebuttal To The Interim Report Issued By The Commission On Lead In The Environment: Lead in Gasoline - A Review of the Canadian Policy Issue.

Prepared by the following American Scientists: Drs. H. Needleman, J.F. Rosen, J. Schwartz and B. Weiss.

I. Neuropsychological Effects of Lead Are Present at "Low Doses."

The report states that many of the symptoms of frank poisoning at blood lead levels above 60 ug/dl are clearly disturbances of the brain and central nervous system. It then goes on to cast doubt on whether studies have demonstrated a relationship between lead exposure at low dose and neuropsychological dysfunction. It singles out the work of one of us (H. Needleman) and then states that a review panel of the U.S. Environmental Protection Agency (EPA) stated that these findings could have had other interpretations. The Commission ignores the fact that the cited EPA report was an unreviewed draft, which was subsequently withdrawn by EPA from its Lead Criteria Document. This occurred after EPA's Science Advisory Board reviewed the reanalyses submitted in response to that critique. The Science Advisory Board stated that Needleman's reanalysis responded to the criticism of the ad hoc committee, and demonstrated that the effects persisted even when reanalyzed as they suggested. Dr. Needleman brought this to the Commission's attention during his presentation in Ottawa; and the EPA also informed the Commission that Needleman's analysis had

responded to the criticism adequately and the critique no longer held! The inclusion of the statement in the Commission's report is more consistent with an attempt to mislead than with an attempt to inform the Minister. We believe that the Commission is obliged to report the latest data to the Minister of Environment, if he is to be able to make a wise decision.

The broad statements in the report are inadequately documented and often at odds with the studies presented to it in Ottawa. For example, the report states that "Data have been produced both supporting and failing to support the effects of body lead on neurobehavioral performance in children." It is remarkable that this report, allegedly interpretive and evaluative, does not cite by title or author, one single study. This deprives the Minister and the reader of the opportunity to judge the basis for this (and many other) assertions. The report states that definitive answers await the results of prospective studies currently in progress. It ignores the fact that two prospective studies were presented to the Commission in Ottawa. The Boston study showed that umbilical cord blood lead levels were related to developmental outcome at 6 and twelve months of age, and the Cincinnati study showed the same association in white offspring. This is but one example of the Commission's selective ignoring of data, which does not support its conclusions.

At frequent intervals, the Commission's report states that "no conclusive evidence has yet been found for neurophysiological effects on the brain at low body levels of lead." At the Ottawa

meeting that we attended, we paid particular attention to the limitations of proof in epidemiological studies, and presented to the Commission the scientific evidence indicating to the objective critic that lesser amounts of lead are neurotoxic. Neurobehavioral abnormalities and electroenchephalagraphic changes at blood lead levels less than 60 ug/dl (and as low as 10 ug/dl) have been noted in many studies, and were described to the Commission.

Sine 1979 10 studies of "low" lead effects on children's IQ have demonstrated exposure-related deficits. The mean effect size of these studies is 0.408. This means that the standard normal deviation of the difference is 0.4. An effect of this magnitude is associated with tripling the rate of severe deficits in children.

II. Neurobehavioral Studies in Animals: Consistency Between Experimental and Human Findings

One of the more dismaying features of the report is the absence of references to the experimental literature, particularly the more recent research. It is especially dismaying because one of the most significant sources of the newer data is the Health Protection Branch of Health and Welfare Canada. There, studies conducted on monkeys by Dr. Deborah Rice and her colleagues have confirmed and extended the conclusions reached by Needleman and others from the human data. Her findings demonstrate advere lead effects at blood levels of 20-25 ug/dl, a range that many Canadian children exceed. The

epidemiological problems cited for the human studies surely play no role in such results. Moreover, the monkey data parallel data obtained in rats with much the same kind of advanced behavioral techniques and that were described at the Ottawa meeting. The consistency of the human and animal findings surely deserved comment.

III. Toxic Biochemical Effects of Lead are Adverse Health Effects in Children

Data were presented to the Commission from several laboratories to indicate that toxic biochemical effects of lead (adverse health effects) have been demonstrated conclusively in children at blood lead concentrations below 25 ug/dl. Such adverse health effects include impairment of basic enzymatic systems related to energy metabolism in cells, detoxification of foreign substances, and interference in neurotransmitter acitivty. Moreover, evidence from 4 Centers (Albert Einstein, Hopkins, Columbia and Harvard) demonstrated that a highly significant percentage of children have positive $CaNa_2EDTA$ provocative tests at blood lead values between 30 to 55 ug/dl. The latter data sets indicate beyond any reasonable doubt that the blood lead concentration per se underestimates the body burden of lead in American children; these data also show tht the magnitude of lead excretion in children with blood lead values noted above is similar in magnitude to children who have higher blood lead values and who thereby qualify immediately for formal chelation treatment.

It is disappointing that the Commission has acknowledged the above data and other toxic biochemical effects of lead in a remarkably tentative manner: to a large extent, these data are dismissed by the Commission because of 1) lack of "substantiation," 2) a small data base in too few children and 3) the lack of obvious clinical symptoms i.e. such impairments in basic physiological and cellular functioning do not constitute adverse health effects produced by lead (see pages X and 20 of the report). These three Commission views are erroneous, cannot be supported by review of the published literature and fail to reflect responsible judgements (based upon detailed evaluation of the data) by regulatory and health agencies in the United States.

To answer the first two opinions presented by the Commission, the data of Piomelli and co-workers (Proc. Natl. Acad. Sci. - 1982) was based upon an analysis of blood lead vs erythrocyte protoporphyrin in 2004 children. The observed threshold for lead effects (14-17 ug/dl) on erythrocyte protoporphyrin clearly provided a "robust" set of data; these data have not been challenged in the biomedical literature. The results of $CaNa_2EDTA$ testing were substantiated independently at four different Centers; and the combined data set in 210 children is by far the largest ever published (Piomelli, Rosen et al, 1984). Lead's impairment of the biosynthesis of the vitamin D hormone, in a dose-response relationship encompassing a range in blood lead values between 12 to 120 ug/dl, is based upon 105 observations (Rosen et al, 1980; Mahaffey, Rosen et al, 1982). These findings have undergone intense scrutiny in the United

States and remain unchallenged in the biomedical literature. Moreover, such effects of lead on vitamin D metabolism in children have been confirmed directly in experimental studies in vivo and in vitro.

Several criteria are readily available to define "adverse health effects" and these are well accepted in the United States (see chapter 13 of EPA's Criteria Document). These include: 1) perturbed function of a specific tissue or organ system; 2) diminished reserve capacity of that tissue or organ system to sustain additional insults; 3) the prevalence of a given effect in a vulnerable group of individuals (such as children); and 4) the net impact of various pertubations that converge together on a single organ or cellular system to impair normal functioning. The toxic biochemical effects presented to the Commission, produced by lead at relatively low concentrations, clearly qualify. These include lead's impairment of heme synthesis, the heme pathway, the cytochrome system, cellular energetics, pyrimidine metabolism, vitamin D metabolism, cellular calcium homeostasis, pertubations in circulating calcium demonstrated in children (see Sorell et al, 1977; Rosen et al, 1980), calcium dependent cellular processes (including calmodulin activated enzyme systems), the hydroxylation of cortisol in children by hepatic microsomal enzymes and so forth.

This extensive but abbreviated list and the interweaving convergence of such lead effects on diverse cell types of different tissues are recognized as adverse by the EPA, the U.S. Public Health Service, and rational and informed pediatricians.

This long list also includes lead's impairment of oxygen transport, detoxification of xenobiotic compounds, neurotransmitter functions and depletion of total body heme. The collective impact of these adverse health effects can be and must be avoided with a wide margin of safety to insure the full growth potential of Canadian children! To do otherwise indicates that a choice was made to sacrifice this potential of Canadian children, until such time as clinically overt, severe and irreversible lead toxicity becomes manifest.

IV. The Relationship Between Lead and Hypertension

The Commission's discussion of the studies relating blood lead to blood pressure suffers from several shortcomings. While in a sense it might seem satisfying to the authors of the Pirkle et al paper that it is the only one discussed, the omission of mention of the other general population epidemiology studies and the large body of animal data gives the impression that there is only one study to evaluate. This leaves the reader with a false impression of the state of knowledge about the subject.

First, the experimental data is of critical importance, because experimental studies control for all of the host of other factors that are more difficlut to manage in a human study. Several different species of animals, exposed to low levels of lead, have all suffered increased blood pressure in multiple experiments by many different laboratories using very strictly controlled protocols. These results remove the question of whether their is causality behind the correlation. Clearly, low

level lead exposure causes increases in blood pressure in rats and pigeons.

Given these data, why would one believe that the same would not hold true for humans? Obviously, the only answer is that humans may react differently to lead because they are different; and the blood pressure response may be species specific, rather than related to any general mechanism. The fact that the blood pressure elevation is seen in several species of animals, however, makes that conclusion questionable even in the absence of human epidemiological data. Moreover, since the experiments also indicate that the mechanism of lead's effect is in the vascular smooth muscle cells and that lead leads to increased intracellular calcium in the cells of those arteries, the mechanism is identified as general and not species specific. Lead has been shown to cause intracellular calcium accumulation in many tissue types in many species; this effect is not one that humans can escape; and change in intracellular calcium homeostasis is the cause of muscle contraction in smooth muscle tissue in general, not just in rats. In particular, it is also true in humans that the higher the intracellular calcium concentration in the smooth muscle cell, the greater is its contraction; and the greater its contraction, the greater is the resistance of arteries to blood flow, and therefore the higher the blood pressure.

In fact, the fastest growing drug for the treatment of hypertension is calcium channel blockers, because they reduce the leakage of calcium into the smooth muscle cells of the vascular

periphery, and therefore lower contraction of the cell and constriction of the artery. Since lead does the opposite of the medication used to lower blood pressure in humans, it can hardly be surprising that lead raises blood pressure.

However, these animal studies, which are completely ignored in the report, are also buttressed by the epidemiological results. These include not merely the papers of Pirkle et al. and Harlan et al., which exhaustively analyzed the NHANEAS II data, but also the other recent general population epidemiology studies, such as Moreau et al., Kromhout et al., and Pocock et al., whose most recent analysis shows p-values for lead of 0.001 in regression analysis.

Even more disturbing than the omission of these results, which all tend to give a consistent picture, is the Commission's assertion that the results are still not "proven." It is first of all worth noting, as was eloquently stated by Sir Karl Popper in Conjectures and Refutations, that no hypothesis can ever be proved true in science; they can only be proven false. When sufficient attempts to prove one false have failed, we accept it until shown otherwise. This acceptance is a gradual and continuous process; and we do not seek to argue over how widely the lead-blood pressure hypothesis deserves to be accepted today. Rather, the question is one of what level of acceptance is necessary, before it is reasonable to take prudent steps to protect public health. This requires a balancing of the costs of being right and the costs of being wrong, as well as the surety of being right. We believe that the abundant animal and

epidemiological evidence, demonstrating that lead causes blood pressure increases in animals, and that lead is significantly associated with higher blood pressure in humans, shows sufficient likelihood of an effect. Given the serious consequences of higher blood pressure, it is manifestly imprudent to allow lead to remain in gasoline while there is a good chance that eliminating it will reduce the number of people with hypertension by over 10%.

To put this in prospective, John Snow is revered as one of the fathers of epidemiology, principally because of his work on water as a source of the cholera epidemics in London. In particular, John Snow studied the geographic pattern of deaths from the disease, and found that they fell off radially in concentric patterns around a particular site on Broad Street. Snow went to that site and discovered a pump connected to a water well. In this case, no laboratory evidence was available (animals were not fed the drinking water to see if they would get sick), and no mechanism was apparent (the germ theory of disease not being current). Indeed, the cholera bacilli was not identified until 30 years later. John Snow is one of the great men of public health, because, at that point, he did the only thing that a reasonable person could do: he took the handle off of the pump! The London political establishment also responded by requiring treatment of water by all water companies, and by restricting their sources. The Commission on Lead in the Environment has grossly failed the same test.

V. The Relationship Between Gasoline Lead and Blood Lead: Is it the Commission's and Minister's Responsibility to Enhance Public Health AT No Cost to Society?

One astonishing omission from the Commision's report is the lack of any discussion of the relationship between gasoline lead and blood lead. This relationship is so strong that it is difficult to reconcile with the conclusion that no further restriction of gasoline lead is necessary. Equally bizarre is the lack of any discussion of the cost savings that will occur if lead levels are reduced, due to the reduction of the corrosive effects of lead on cars, although the cost of removing the lead from gasoline is discussed. These two omissions seriously imbalance the report. Equally incredulous in a document specifically directed to gasoline lead is the omission of any reference to or discussion of EPA's analysis of the impact of its gasoline lead regulation, The Costs and Benefits of Reducing Lead in Gasoline. EPA's criteria document, which provides the background for regulation of stationary sources of lead, is referred to, but a 500 page analysis of the exact issue that the Commission is addressing is completely ignored! The Commission was supplied with several copies of this document by the EPA. It is not common practice in science to ignore papers, analyses and data that point to conclusions that one wishes to avoid. The two omissions mentioned above are discussed at length in the document that the Commission refuses to recognize.

The relationship between lead in gasoline and lead in people is well established by both human epidemiology and experimental

isotope studies. The NHANES II data showed a strong relationship between blood lead and gasoline lead ($p < 0.000001$), after controlling for age, race, sex, income, family size, degree of urbanization, residence inside center city, region of the country, occupational exposure, smoking, alcohol consumption, dietary food intake, lead used in canned foods, and so forth. The same relationship (also with a t-statistic of 11) was found after analyzing the data from the Chicago blood lead screening program for children, after controlling for race and age. New York's and Louiville's screening programs showed the same relationship; and the CDC data for the national screening program showed a correlation coefficient of 0.80 between the percent of children with high blood lead levels and gasoline lead! Isotope studies by Manton and Terra in the United States have shown the same results; and the Italian isotope study found that when the isotopic ratio of lead in gasoline was deliberately changed, the ratio in people's blood lead levels began to change as well; the ratio was still changing when the isotopes in gasoline were switched back, but already indicated <u>at least 6 ug/dl</u> came from gasoline lead.

Some have argued that because recent blood lead levels in Canada in 1984-1985 are lower than blood lead levels in the U.S. in 1978 (the mid year of NHANES survey), that EPA"s recent action further reducing gasoline lead levels was necessary, but that further action in Canada is not. This ignores the main point of the NHANES II lead analysis, which is that <u>lead levels were falling in the U.S. due to the decline in gasoline lead use</u>.

Gasoline levels in 1984-85, when EPA decided to tighten its lead in gasoline rules, had fallen substantially from 1978, and using the well established relationship between gasoline lead and blood lead, EPA predicted that mean children's blood lead levels would be down to about 10 ug/dl. This is very similar to the recent results in Ontario; and all of the benefits of further reductions in gasoline lead level that are discussed in The Costs and Benefits of Reducing Lead in Gasoline are for reductions below that new baseline. The recently released figures on the mean blood lead levels for Hispanic children in 1983 (from the Hispanic HANES) confirm that U.S. blood lead levels were down at or below 10 ug/dl in the mid 1980's, which is very similar to the Canadian levels. This is precisely the drop predicted from the relationship between blood lead and gasoline lead levels that was derived, when mean blood lead levels in children were 17 ug/dl!

While the Commission's principal charge was health, it did find time to discuss the cost of further tightening of the gasoline lead standard. It cites a number of estimates, mostly from industry, indicating that reduction to the new U.S. lead level would cost several cents per gallon. It omits all mention of the fact that lead leads to faster corrosive wear in mufflers, carburetors, engine parts, spark plugs, and that the cost of this wear is also several cents per gallon. The ignored EPA analysis of the proposal to tighten gasoline lead standards demonstrated, after extensive analysis, that the maintenance savings from switching to low lead fuel would completely offset the higher manufacturing costs! This analysis survived extensive scrutiny

in formal rulemaking procedures in the United States, and indicates that the net cost to consumers of reducing the amount of lead in leaded gasoline is approximately zero.

This places the health effects avoided in an entirely different light, because the cost of avoiding those health effects is zero. The public policy question then becomes whether those free health benefits will be accepted, or whether they will be turned down. This is an entirely different question to be posed to the Minister than the one posed by the Commission's interim report.