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REVIEW

Clair Patterson and Robert Kehoe: Two Views of Lead Toxicity

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INTRODUCTION

In the early struggle to regulate airborne lead in the environment, two dominant figures emerged. Robert Kehoe was the lead industry's designated spokesman. At his antipode was Clair Patterson. These two men, the avatars of the industrial and public health outlooks, vividly define the 80-year contest to control lead in the environment. In examining the personalities embedded in the struggle to regulate lead we can hope to understand why it took 2 years to put lead into gasoline and 60 years to take it out.

THE INTRODUCTION OF LEAD INTO GASOLINE

In 1921 General Motors lagged badly behind Ford's Model T in sales, and GM's flagship vehicle, the Cadillac, had an engine knock. General Motors' C. F. Kettering chafed in second place. He set his lab on an urgent search for an antiknock agent. When GM found an old German patent, tetraethyl lead (TEL), that silenced the knock in their laboratory engine, a new industry was born. GM and DuPont, already interlocked, joined forces to produce the additive and called their fuel mixture "Ethyl Gasoline." It is clear that the company was worried about the toxic properties of their product; the word "lead" appeared nowhere on the label.

In the Indianapolis 500 in 1923, ethyl fueled the first three winners. Production of TEL, under three separate companies, began in three plants: Standard Oil was licensed to produce TEL in northern New Jersey, DuPont in southern New Jersey, and GM in Dayton, Ohio.

Shortly after production began, workers in all three plants began to go crazy and die, often in straightjackets. Somewhere between 13 and 15 known deaths occurred, and over 300 men became psychotic. Workers called the product "looney gas" and the place where it was fabricated "The House of Butterflies." This last sobriquet was earned by the sight of psychotic workers trying to brush phantom insects off of their arms.

A moratorium on the use of TEL was called and the Surgeon General convened a meeting of industrialists, public health specialists, and academic physicians to determine if this new product was a serious enough threat to be banned or whether it could be sold to the general public.

KEHOE'S POSITION ON LEAD TOXICITY

At the Surgeon General's meeting, a young assistant professor of pathology at the University of Cincinnati, Robert Kehoe, emerged as the principal industrial expert and spokesman. When workers died in the Dayton plant in 1923, General Motors asked Kehoe to consult and make preventive recommendations. He made some measurements of lead levels in the plant and in workers directly exposed to TEL. His control group were workers in the plant who had no direct contact with the compound.

This assignment marked the beginning of a major career shift for Kehoe. C. F. Kettering would, with support from the Ethyl Corp., DuPont, and others, open the Kettering Laboratory on the University of Cincinnati Medical campus and name Kehoe as its director. Kehoe would also become Medical Director of the Ethyl Corp. and a corporate officer at GM. In the Surgeon General's meeting and others that followed his words were put forward as the final opinion on lead by the industry representatives, and he was treated with considerable deference. Kehoe was not burdened with a hypertrophied sense of modesty. He spoke with great confidence that his data was the best, if not the only, guide to the truth.

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Virtually the only source of research support on lead for the next 50 years would come from industrial treasuries, and most of it was directed to Kehoe. As a result he held an almost complete monopoly on lead data. To these he gave his singular and somewhat oracular interpretation. He found lead in the blood of workers in Dayton who did not handle TEL and concluded that lead was a "normal" constituent of the human body. When challenged on the grounds that his control group was contaminated, he traveled to Mexico, found a rural village outside of Mexico City, and measured lead in soil, food, tableware, and water of the residents. From them he took blood, urine, and feces. He found measurable amounts of lead in the dishware. He found lead in the residents and reported, again with great confidence, that this proved that lead was a "normal" part of the body. That Mexican tableware is a dangerous source of lead is a well-known fact. Kehoe offhandedly dismissed this troublesome finding.

This assertion, that lead was a "natural" component of human biochemistry, was the fundamental strut in Kehoe's constructed case that lead poisoning is a relatively rare event, restricted to some factory workers, and that lead in gasoline presented no threat to human health. It became the fulcrum of the debate between him and Patterson.

In Senate hearings on the Clean Air Act in 1966, Kehoe was one of the important witnesses before the Muskie Subcommittee on Air and Water Pollution. Before Kehoe testified, the Surgeon General, William Stewart, had put on record, perhaps for the first time, the government's concern about the effects of lead at low doses and pointed to the vulnerability of children and pregnant women (Committee on Public Works, 1966, p. 118):

> However, there is evidence suggesting that lower levels of exposure produce more subtle but potentially serious effects on human health. Existing evidence suggests that certain groups in the population may be particularly susceptible to lead injury. Children and pregnant women constitute two of the most important of such groups. Some studies have suggested an association between lead exposure and the occurrence of mental retardation among children.

Then Kehoe testified. He began by informing the chairman that he knew so much of the subject that he was forced to leave a great deal of information out, otherwise, "I am afraid we would be here the rest of the week ..."

Kehoe said that enough was known about TEL toxicity to allow the amount of TEL to be increased without risk: "The fact is, however, that no other hygienic problem in the field of air pollution has been investigated so intensively, over such a prolonged period of time, and with such definitive results."

Muskie pointed out that the Public Health Service and others disagreed and that there were unanswered questions and need for more research.

> *Kehoe*: ... I would simply say that in developing information on this subject, I have had a greater responsibility than any other persons in this country ... the evidence at the present time is better than it has been at any time that this is not a present hazard.

Muskie pressed on about finding a substitute for TEL: " ... would it be desirable if a substitute for lead could be found for gasoline?"

> *Kehoe*: There is no evidence that this has introduced a danger in the field of public health ... I may say the work of the Kettering Laboratory in this field, that lead is an inevitable element in the surface of the earth, in its vegetation, in its animal life, and that there is no way in which man has ever been able to escape the absorption of lead while living in this planet. (Committee on Public Works, 1966, p. 206)

Kehoe asserted that air lead levels had decreased in Cincinnati. Muskie pointed out what appeared to be a paradox in Kehoe's statement:

> Over the past 30 years I assume there has been a tremendous growth in automobiles and in the amount of traffic in Cincinnati, and yet as I understand it, you say that there has been no increase in the concentration of lead in the ambient air?
>
> *Kehoe*: That is a fact, There has been a change downward, since the period of the Second World War ... we had difficulty in Cincinnati getting the kind of coal that we would like .... During this period we had to take the coal that could be obtained .... In 1945 this whole situation was changed and in the period immediately following this the lead content of the atmosphere of Cincinnati went significantly downward.
>
> *Muskie*: What you have just said is that the decrease in the concentration in the atmosphere is due to better control of stationary sources of air pollution?
>
> *Kehoe*: That is right.
>
> *Muskie*: Have you drawn any conclusions as to whether or not the concentration of lead in the atmosphere has gone up, gone down, or remained stationary?
>
> *Kehoe*: We conclude that there has been no increase.

Kehoe neglected to mention that the Cincinnati studies were biased. In the early years of air lead measurement, more samples were taken from industrial sites, and fewer industrial sites were sampled later. This may have been enough to account for the downward trend.

> *Muskie*: Is it your conclusion that in 1937 to the present time, on the basis of that data, that there has been no increase in the amount of lead taken in from the atmosphere

by traffic policemen, by attendants at service stations or by the average motorist?

Kehoe: There is not the slightest evidence that there has been a change in this picture during this period of time. Not the slightest.

Nothing could displace Kehoe from his unlimited confidence and optimism. When Muskie again returned to Kehoe's claim that there was no harm to be expected from atmospheric lead, he got a characteristic response.

Muskie: Does medical opinion agree that there are no harmful effects and results from lead ingestion below the level of lead poisoning?

Kehoe: I don't think that many people would be as certain as I am at this point.

Muskie: But you are certain?

Kehoe: ...It so happens that I have more experience in this field than anyone else alive.

Kehoe's sway in lead toxicology held until the late 1960s. The durability of the extraordinary scientific solecism that lead in the body was natural is a testament to the shielding power of reputation. It pays to advertise.

CLAIR PATTERSON'S ROLE

There were no scientific challengers to Kehoe until Clair Patterson. His methods and conclusions could not have been more different. Patterson aimed his attack at Kehoe's assertion that lead was a normal component of the human body, insisting that what he called "normal" was in fact "typical."

This was more than a semantic quarrel. Patterson fundamentally altered the vocabulary with which the debate over the health effects of lead was conducted. Most people, following Kehoe's arguments, referred to "normal levels" of lead in blood, soil, and air, meaning values near the average. They assumed that because these levels were common, they were harmless. "Normal" also carries some of the meaning "natural." Patterson argued that "normal" should be replaced by "typical." Simply because a certain level of lead was commonplace did not mean it was without harm. "Natural," he insisted, was limited to concentrations of lead that existed in the body or environment before contamination by man.

Kehoe and other workers in lead completely missed this distinction because their reagents, instruments, and the very air in their laboratories were freighted with lead. As a result the baseline measurements of all their samples were raised and their results blurred. In addition, the control subjects in Kehoe's studies, the workers in the Dayton plant who did not directly handle TEL, were nevertheless exposed to it. His second "unexposed" group, the Mexican farmers, ate food that had been cooked in and served from lead-containing ceramic pots and plates.

Patterson was able to demonstrate and correct this fundamental error because of the extraordinary measures he took to avoid contamination of his specimens. Because his lab was cleaner than others, his measurements of isotopic ratios were free of the contamination that confounded the findings of Kehoe and others. Where Kehoe measured lead in "unexposed" workers in a TEL plant and Mexican farmers, Patterson studied pre-iron age mummies and tuna raised from pelagic waters.

Patterson stumbled on the problem of global lead contamination while measuring the concentration of mineral isotopes in his study of the age of the earth. He noticed that the lead levels in his reagents and in soil and ice were much higher than predicted by theory. It would have been understandable if he treated the contamination of his reagents as a severe annoyance to be overcome and then forgotten, but that was not his style. To him it was not a nuisance but a clear signal of the contamination by lead of the biosphere. This was an unrecognized danger, he believed, to everyone. In this regard, he provided facts to flesh out the warnings 40 years earlier of Yandell Henderson, David Edsall, and Alice Hamilton. These health scientists predicted at the Surgeon General's 1925 meeting that tetraethyl lead would lead to widespread increases in human lead burden.

Patterson began to divert a considerable proportion of his extraordinary mind and energy away from pure geochemistry to the study of lead contamination. By conducting his experiments in his ultraclean chamber in which the air was filtered, the experimenters gowned and masked, and the reagents and water supply purified of any trace of lead, he was able to avoid contamination and establish the true concentrations of lead in his samples. He showed that technological activity had raised modern human body lead burdens 100 times that of our pretechnologic ancients. In addition to tuna caught in the deep strata of the Pacific Ocean and brought to the surface with great care to avoid contamination on the way up and pre-iron age mummies buried in sandy soil, he sampled cores of the Greenland ice pack. By slicing the ice cores he was able to precisely date the specimen and show the time course of lead in the atmosphere.

In 1965 the Editor of the *Archives of Environmental Health*, Kathryn Boucot, invited Patterson to

write an editorial on lead pollution. He submitted instead a long article entitled "Contaminated and Natural Lead Environments of Man" based on his findings and speculations. Kehoe was one of those selected to review his manuscript and decide whether it should be published. Kehoe argued that the paper be accepted for publication for ironic reasons:

> I should let the man, with his obvious faults, speak in such a way as to display these faults .... The inferences as to the natural human body burden of lead, are I think, remarkably naive .... It is an example of how wrong one can be in his biological postulated and conclusions, when he steps into this field, of which he is so woefully ignorant and so lacking in any concept of the depth of his ignorance, that he is not even cautious in drawing sweeping conclusions. This bespeaks the brash young man, or perhaps the not so young [Patterson was 43 at the time] passionate supporter of a cause. In either case hardly the mark of the critical investigator.
>
> We have been working with the physiological aspects of this problem carefully and step by step for more than thirty years ... It is disappointing that our work has not been viewed in this manner by Dr. Patterson, but the issue which he has raised, in this article and by word of mouth elsewhere, cannot be "swept under the rug."
>
> The virtue of the paper is its examination of the manner in which man has altered "the face of the earth" in a variety of ways, and has disturbed the composition of the human internal milieu in so doing. It is strange that Dr. Patterson does not realize that this has happened to the large proportion of mineral components of the earth, and that this is one of the outstanding physiological problems of our time. Can we adapt to these changes, individually and collectively? Are our physiological mechanisms flexible enough to cope with them? It appears, in the case of lead, that they are ... (letter from R.A. Kehoe to K. Boucot, April 16, 1965)

This last sentence declares his second fundamental conflict with Patterson. Kehoe claimed that mankind has adapted to environmental lead. Patterson's precise point was that man had recently increased the concentration of lead and that the short span of exposure, a few thousand years, was an instant in the Darwinian time scale, nowhere near the time needed to develop adaptive responses.

Patterson's paper unleashed a fusillade of angry responses from the toxicological establishment. The rage was fueled by his hubris in stepping outside of his field and talking about humans instead of rocks. It extended to the Editor of the journal, whose judgement was attacked for publishing the paper. Patterson wasn't bothered at all by public criticism; he seemed to thrive on it.

But there were more serious measures. He was visited by a group from Ethyl Corp. who tried to (in his words) "buy me out through research support that would yield results favorable to their cause." He answered with a lecture in which he predicted that future scientists would show that Ethyl's activities were poisoning the environment and people and that this would result in the shutting down of their operations. After this meeting, his long-standing contract with the Public Health Service was not renewed, nor was his substantial contract with the American Petroleum Institute. Some members of the Board of Trustees at California Institute of Technology visited the chairman of his department and tried to get him fired (letter from C. Patterson to H. Needleman, August 5, 1992).

One week after Kehoe, Patterson testified before the Muskie subcommittee. He began by challenging the conventional wisdom that natural lead cycling and human activity contributed roughly the same amount of lead to the environment. He pointed out that 10,000 tons of lead were naturally recycled each year, while millions of tons were emitted due to industrial emissions. He believed that large numbers of people are sickened as a result of this unnatural load. Prophetically, he emphasized the central nervous system as a target. Patterson was not reticent: he pointed out that when public health agencies collaborate with polluting industries to decide whether public health is threatened by their products, the results are often absurd.

When Muskie asked him if his classification of "natural," "typical," and "contaminated" concentrations of lead in food and humans was a logical approach to follow, Patterson's response was pointed: "Not if your purpose is to sell lead."

> *Muskie*: Well, I don't think it is the purpose of the Public Health Service to sell lead.
>
> *Patterson*: That is why it is difficult to understand why the Public Health Service cooperated with the lead industry in issuing this report which fails to make this distinction.
>
> *Muskie*: That is the Tri-City Study?
>
> *Patterson*: Yes.
>
> *Muskie*: Have you discussed this with the Public Health Service?
>
> *Patterson*: Yes.
>
> *Muskie*: What is their reaction?
>
> *Patterson*: I have both friends and antagonists in the Public Health Service.
>
> *Muskie*: I think I do too.

Muskie was determined to throw Kehoe's industry perspective into contrast with the public health perspective. Patterson was the right man for this task.

> *Muskie*: ... those representing the industry, the American petroleum industry and others, have told us that there is no evidence of increase in the past since sometime in the 1920's that create any cause for concern as to hazards from lead .... Now what do you say on this and where is their analysis faulty?
>
> *Patterson*: The evidence for an increase in concentration the blood of people in American cities is clear. The difference, as I said, between the concentrations of lead in blood of people living in cities and outside of cities is that between 0.17 and 0.11 parts per million. The difference is not due to food .... As I say from these known things we can predict that the people in the cities will have higher concentrations of lead in their blood as a consequence of their absorbing the greater amounts of lead and the difference is due to the greater concentration of lead in the air.

He attacked Kehoe's claim that levels had dropped in Cincinnati:

> ... there is given on the back side of the page of data from which Dr. Kehoe quoted, another figure which shows that concentrations of lead in that very same city increased. This is data gotten from the National Air Sampling Network which is not the same organization that Dr. Kehoe represents. It shows an opposite trend. The point here is that those kinds of data which purport to show that the concentrations of lead in the atmosphere of American cities is decreasing is rather invalid.

After having elicited clear contradictions of Kehoe's claims that lead levels had not changed, Muskie focused attention on the other critical issue. Industry had measured the prevalence of lead toxicity by counting deaths, or at least severe damage to the brain. Muskie raised the question of a larger pool of unrecognized toxic illness: "Is it conceivable that there is something different in the deleterious effects on health from low-level exposure than from more concentrated exposure leading to classical lead poisoning?"

> *Patterson*: ... when you expose an organism to a toxic substance it responds in a continuum, to continuously changing levels of exposure to this toxic substance. There is no abrupt change between a response and no response. Classical poisoning is just one extreme of a whole continuum of responses of an organism, human organism, to this toxic metal. There is a reason why this shouldn't be so.

Here is another point in which Patterson's point of view strongly departs from Kehoe's, and here again Patterson is on firm scientific ground. Kehoe treated lead poisoning as a "yes-no" phenomenon: you have it or you do not. Patterson admitted the dose–response relationship to the question and treated toxicity as a dimensional trait: there are degrees of poisoning. This is of course a more sophisticated and rigorous way of examining the data.

Muskie's aggressive inquiry began the government's shift away from passive complacency toward lead. The hearings focused awareness on increasing levels of lead in air, and taking Patterson's point, established the idea that lead poisoning was not only a florid disease of workers, but also could be an insidious, silent danger.

THE NATIONAL ACADEMY OF SCIENCES REPORT

In 1970, the EPA, under pressure to regulate lead in gasoline, funded a study of airborne lead and its health effects by the National Research Council. Kehoe was named a consultant. From the beginning, other questions were raised about the fairness of the NAS committee. The committee and its consultants were chosen by an informal "Old Boys' Network." NAS staff solicited nominations for the committee from associates and people they knew and trusted. The results in this case were suspect. No member of the committee or its consultants had worked on airborne lead. Four eminent scientists with long experience in lead, who were obvious choices, were not selected. In addition to Patterson, the excluded scientists were John Goldsmith, head of the California Health Department's division of Epidemiology; Harry Schroeder at Dartmouth, who had conducted some of the only transgenerational studies of lead at low dose; and T. J. Chow, who studied atmospheric lead deposition as measured in Greenland ice cores. All of these men had done important work on the subject, and all were on the alarmist side of the balance. These omissions were obvious to many people, and the Academy became defensive. One Academy Staff member told a *Science* magazine reporter that Goldsmith and Schroeder were thought to be potentially disruptive to the work of the committee.

The committee appointed a large number of consultants. Heavy industry representation was obvious. Kehoe and Lloyd Tepper came from the Kettering Lab. Gordon Stopps, Kamran Habibi, and John Perrard were from EI DuPont, and Gary Ter Haar came from Ethyl Corp. Chow was appointed as a consultant. The committee gave the industry scientists major responsibility for writing sections of the draft. Stopps, whose earlier publications had for years claimed that TEL was harmless, was asked to write two important sections in the book: adult epidemiology and lead alkyls.

This did not go down easily. Harriet Hardy, an eminent expert in metal toxicity, complained about the imbalance and bias of the panel. T. J. Chow

wrote about conflicts of interest encountered in asking industry employees to write chapters on their products. The Academy staffer responsible for this project responded "Rosters of committees and panels consist of people with high competence in specific fields regardless or where they work and the appointment is made with the understanding that the person is thought to serve as an individual and not as a representative of his organization . . . ." This understanding did not seem to extend to Patterson, Goldsmith, or Schroeder (Boffey, 1975).

The NAS report, "LEAD: Airborne Lead in Perspective" (National Academy of Sciences/National Research Council, 1972) was a failure. It spent many pages on discussions of lead in plants and animals, but evaded a full examination of the questions for which it had been commissioned. It said that there were no conclusive data to show that atmospheric lead at concentrations below 2 μg/M3 contributed to blood lead levels, nor was there any evidence to support toxicity at low levels of lead. The lead industry trumpeted it, proclaiming that the prestigious scientific body had given lead a clean bill of health.

THE SECOND NAS REPORT

Eight year later, the National Academy of Sciences convened another committee to study the health implications of environmental lead (National Academy of Sciences/National Research Council, 1980). This time Patterson was elected to serve as a member. His viewpoint about the universal contamination of the biosphere by industrial activity received careful but respectful attention in this later publication, but he was not satisfied. He succeeded in having an entire chapter of his dissenting opinion inserted in the book. He clarified his argument through the use of Fig. 1: (a) represents the lead content of a human body before the iron age, (b) represents the content of a 20th century American, and in (c) represents the content of lead in the body of a patient with classical lead poisoning. Patterson stated that between 1850 and 1923 it was believed that the amount of lead in (b) was thought to be the amount of lead in (a). Americans were thought to have virtually no lead in their bodies. After Kehoe published his findings, it was believed that the amount of lead in (a) was represented by (b); the "natural" amount of lead was that typically found in humans. Patterson, through his studies, established that the "natural" amount of lead was that in (a).

Patterson's personal review of the technological history of our planet, his criticism of traditional thinking and analytic methods, and his view of the evolution of competing world views—the manipulative engineering view and the later evolving humanitarian world view—make interesting, if difficult, reading. He argued that modern intracellular levels of lead were so high as to make it highly probable that deleterious effects were occurring. This is of course of semi-scientific statement, as he would have been the first to state if someone else had uttered it. He pointed out the difficulties encountered in studying cellular interactions with lead and the need for lead-free systems in which to conduct them. He posited that biochemical systems that employ calcium are likely to be sensitive to lead perturbation. Eight years later, Marcovac and Goldstein would validate this prophecy by showing that intracellular protein phosphokinase-c, a calcium-dependent part of the second messenger sys-

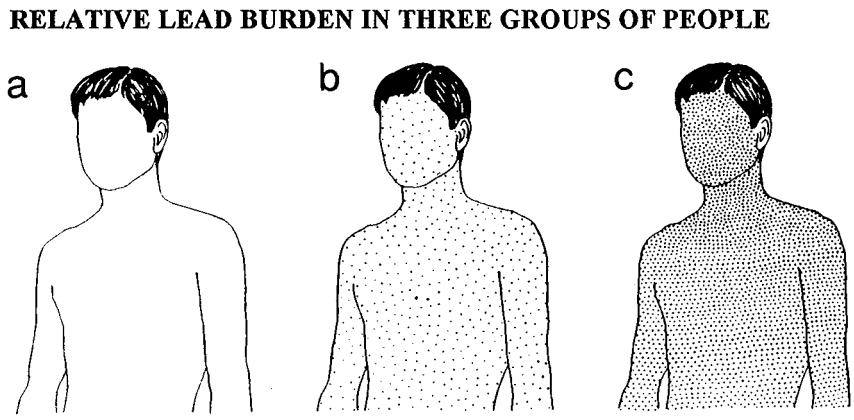

FIG. 1. (a) Prehistoric, uncontaminated groups; (b) Present-day Americans; (c) Lead-poisoned individuals.

tem, is stimulated by lead at lower concentrations than calcium (Markovac and Goldstein, 1988).

The final section of Patterson's statement chides the committee on which he served. "It is intrinsically wrong to mine and smelt a highly toxic substance such as lead on a scale of millions of tons per year and then disperse it within human environments. The majority of this Committee on Lead … fails to explicitly acknowledge this obvious truth …" He recommended the phasing out in "as short a time as feasible" the manufacture of lead in any product that disperses it. He pleaded for research in the how to apply humanitarian principles to guide future developments in engineering technology: "something which has never occurred before in human history." Patterson saw lead poisoning as a window through which to understand and fix our modern dilemma. "The presence or absence of certain vital kinds of knowledge from these fields may very well turn out to be the factor which tips the scale for or against the survival of our hominid species in the face of challenges presented by impending developments in genetic engineering."

A great deal of research has been completed since the Muskie hearings and the NAS report. Almost all of it has borne out Pat's predictions. With the removal of lead from gasoline, blood lead levels in children and adults have declined by 80%. The mean blood lead level of American children, which was 15 μg/dl in 1978, is now 3.6 μg/dl. Many people regard this as one of the most important public health triumphs of the past 3 decades. At the same time, better quality studies have shown effects of lead on children's psychological performance at lower and lower levels. Work remains to be done.

Many people have felt the scorn of Patterson's criticism, and been scorched by his unceasing demands for excellent work. Almost all have come to admire his steadfastness and prescience. To me he was a warm and simple man, often funny, always gracious and in some ways naïve about the workings of the world.

It is clear that Patterson was the primary scientific force in altering the narrow world view of lead toxicity. This immovable man's insight enabled him to see in the troublesome contamination of his specimens not a technical laboratory difficulty to be solved, but a clue to a widely ignored public health problem of tragic dimensions. Having seen it, he was confronted with an inescapable urge to redress the 70-year-old error that permitted the introduction of tetraethyl lead into gasoline and its products into the bodies of millions of citizens. The blood lead levels of today's children are a testimony to his brilliance and integrity.

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