Journal of Amer. Medical Assn. 84 (May 16, 1925) 1481-86.

...rvals of three months, six months, ...ne and one-half years. In each case the ...re negative.

CONCLUSIONS

The results reported show the practical value of scarlet fever toxin used in skin tests for susceptibility and active immunization for the prevention of scarlet fever.

It has been demonstrated that the toxin may be administered with safety in doses large enough to confer complete immunity.

Active immunity is developed within two weeks, and it lasts at least a year and a half.

TETRA-ETHYL LEAD

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A new problem of public health and of industrial hygiene has suddenly arisen in this country as a result of the addition of tetra-ethyl lead to motor car gasoline. This procedure was adopted about two years ago, but it did not come to the knowledge of the general public until last fall, when a number of men were poisoned in a New Jersey plant and five died. The distressing details of these cases of insanity and death and the unknown nature of the new poison aroused much excitement and alarm, and induced the public health officials of New York City and of the states of New York and New Jersey to forbid the use of "ethyl gasoline" on the ground of danger to the public from poison contained in exhaust gases of motor engines burning such gasoline.[1] This prohibition has recently been rescinded in the two states, but is still in force in New York City.

Public excitement soon subsided, but a large and continually growing body of mechanics now organized in the Unions of Automobile and Aircraft Mechanics, Teamsters and Chauffeurs became increasingly concerned over the possible danger to them, working as they do in an atmosphere of exhaust gases, and, finding a dearth of authoritative information on this phase of the matter, they applied to the Workers' Health Bureau for advice. The present report was compiled from the available data at the request of the Workers' Health Bureau and with the assistance of the bureau.

Tetra-ethyl lead is added to gasoline to eliminate the "knock" or detonation in internal combustion engines. A halogen "carrier," either ethylene dibromid or trichlorethylene, is added, and during combustion decomposition occurs, with the formation of lead chlorid or lead bromid, together with lead sulphate from the sulphur in the gasoline and also small amounts of lead oxid and metallic lead. The problem, therefore, concerns two distinct dangers: that of tetra-ethyl lead itself, and that of the lead products resulting from its combustion.

TOXICITY OF TETRA-ETHYL LEAD

Harnack,[2] in 1878, tested the toxicity of triethyl lead and its acetate on frogs, rabbits, cats and dogs. Years after, in 1921, Mason[3] of Cincinnati confirmed many of Harnack's findings, using various salts of triethyl and trimethyl lead. The most important features of these experiments are: a stimulating action on the central nervous system, mainly the medulla and higher centers; a marked stimulation of the central motor nerve mechanism, evidenced by trembling, twitching and, finally, convulsions, but without loss of consciousness; an extreme fall of blood pressure, apparently central in origin, for it fails in pithed animals; changes in the respiration, which at first is stopped, and then accelerated and deepened; slowing of the pulse, and increased peristalsis with colic and diarrhea.

The symptoms set up by tetra-ethyl lead, in animals and in human beings, bear a striking resemblance to this description, as can be seen in the report of a study of the latter recently completed by Eldridge[4] of the Chemical Warfare Service. From these experiments it is also evident that tetra-ethyl lead can be absorbed through the skin and through the respiratory tract, and that there is a cumulative effect when repeated sublethal doses are administered.

Briefly summarized, Eldridge's findings are as follows: Experiments on six dogs showed that application of tetra-ethyl lead to the shaved skin of the abdomen resulted in a direct action on the intestinal tract, characterized by acute lead colic, followed by diarrhea, the abdomen tense and painful to pressure, then depression, difficulty in getting up on the legs, tremors, coma, convulsions and death. The lethal point for dogs by skin absorption was found to be 0.3 c.c. per kilogram of body weight.[5] Death followed in four dogs after from twenty-four to 180 hours, two recovering. In eleven guinea-pigs the lethal amount was determined to be 0.6 c.c. per kilogram of weight, and death came on in from twelve to sixty hours. Three of this group recovered. The symptoms were similar to those in dogs.

Inhalation experiments were made on mice, five animals being used for each of ten concentrations of tetra-ethyl lead. The exposure lasted ten minutes, and during this time the mice showed activity, followed, after removal from the test chamber, by marked excitement, then depression, collapse, trembling, convulsions and death. The lethal dose overaged 5.11 mg. per liter of air.

To determine possible cumulative effects, a 4.08 kg. dog was chosen, and applications of 0.1 c.c. were made to his skin once a day. After the twelfth application the dog became depressed and nervous, and increasingly so until the eighteenth, when he became unsteady on his feet and trembled. He died forty minutes after the twenty-first application. The cumulative action was also tested on mice, by inhalation experiments, exposing ten of them to 0.5 mg. per liter of air for ten minutes a day. Five died, on the fourteenth to the twentieth days.

Necropsies on the dogs dying with acute poisoning showed an acute inflammation of the small and large intestines, with numerous ulcers from 1 to 1.5 cm. in diameter, clean and punched out, with a smooth base. These were chiefly in the region of Peyer's patches, which were swollen and prominent. One animal had a similar ulcer near the pyloric end of the stomach; one had no lesion in the intestinal tract at all. There was no change in the heart, lungs, liver or spleen, but a mild congestion in all zones of the kidney. Analyses were

1. An editorial in THE JOURNAL, Nov. 8, 1924, p. 1511, called attention to tetra-ethyl lead as "another industrial hazard," and, after commenting briefly on a number of fatalities among the producers of this substance spoke also of the possibility of poisoning from the exhaust gases of motors, particularly as lead is a cumulative poison.
2. Harnack: Arch. f. exper. Path. u. Pharmakol. **9**: 152, 1878.
3. Mason, E. C.: The Pharmacologic Action of Lead in Organic Combination, J. Lab. & Clin. Med. **6**: 427 (May) 1921.
4. Eldridge, W. A.: A Study of the Toxicity of Lead Tetra Ethyl, Report 29, Chemical Warfare Service, Oct. 5, 1924.
5. Or 0.498 gm. per kilogram of weight. One cubic centimeter of pure tetra-ethyl lead weighs 1.659 gm.

made of excretions, organs and bones of dogs and guinea-pigs, and lead was found in both urine and feces, in skeleton, intestines, liver and lungs, by far the largest amount being in the skeleton.[6] Eldridge comments as follows:

> We are dealing with a highly lipoid-soluble lead compound, which is capable of skin penetration and which, furthermore, is comparatively stable. It is probably the only compound which, absorbed through the skin, causes acute lead poisoning.

As a preventive, washing with various substances was tried. Although common soap and olive oil were both found to work well, the best agent was kerosene, followed by tincture of green soap. Animals so treated survived even if thirty minutes elapsed before washing the skin.

This is Eldridge's summary:

> It is quite evident from these observations that the manufacture, handling and distribution of lead tetra-ethyl involves considerable danger to operatives, of acute lead poisoning in those instances where considerable material is splashed upon the skin, and of chronic lead poisoning from the absorption of small amounts by inhalation, by the skin or by the mouth.

THE PRESENT-DAY PROBLEM

There are four questions that must be answered before we know whether the manufacture and distribution of tetra-ethyl lead and its use in gasoline carry with them a danger serious enough to warrant prohibition by public health authorities.

1. The danger to men engaged in the manufacture of tetra-ethyl lead.

2. The danger to men handling ethyl fluid. This is a mixture of tetra-ethyl lead and ethylene dibromid or trichlorethylene, with the addition of a small quantity of dark colored dye. Ethyl fluid is handled by employees in the production plant and by distributing and filling station employees, who mix it with gasoline.

3. The danger to men handling ethyl gasoline. This is ordinary gasoline to which a small amount of ethyl fluid has been added, about one-half teaspoonful to the gallon.

4. The danger to the public from breathing the exhaust gases from engines using ethyl gasoline, and the danger to garage workers, chauffeurs or other persons who work on engines, exhausts or mufflers of motors burning ethyl gasoline.

1. *The Danger to Men Manufacturing Tetra-Ethyl Lead.*—Within the last seventeen months, eleven men have died and one man has become insane through tetra-ethyl lead poisoning. All were engaged in the manufacture of this compound. These accidents occurred as follows:

Sept. 21, 1923, one death, E. I. du Pont de Nemours & Co., Carney's Point, N. J.

June 1, 1924, two deaths, General Motors Research Corporation, Dayton, Ohio.

July 14, 1924, one death, E. I. du Pont de Nemours & Co., Carney's Point, N. J.

Oct. 20, 1924, one death, E. I. du Pont de Nemours & Co., Carney's Point, N. J.

Oct. 28-30, 1924, five deaths, Standard Oil Company, Bayway, N. J.

Feb. 18, 1925, one death, E. I. du Pont de Nemours & Co., Carney's Point, N. J.

Feb. 18, 1925, one insane, Standard Oil Company, Bayway, N. J.

6. The distribution in one dog was: bone, 200 mg.; intestines 96 mg.; liver, 76 mg.; lungs, 16 mg.; no other organ had so much as 10 mg.

Eldridge's paper contains a summary of the symptoms in the Standard Oil cases, as reported to the company by W. Gilman Thompson and A. W. Schoenleber, May 16, 1924. The first symptom noticed is a marked fall in blood pressure, sometimes 60 mm. of mercury below normal, an accompanying fall in body temperature, which has been as low as 94.6 F., and a low pulse rate, down to 48 a minute. Then symptoms of profound cerebral involvement appear, persistent insomnia, extraordinary restlessness and talkativeness, and delusions. The gait is like that of a drunken man, but there are no paralyses or convulsions. Finally, after a period of exaggerated movements of all the muscles of the body, with sweating, the patient becomes violently maniacal, shouting, leaping from the bed, smashing furniture, and acting as if in delirium tremens; morphin only accentuates the symptoms. The patient may finally die in exhaustion. In two fatal cases, the body temperature rose to 110 F. just before death occurred. One of these was a young man of fine physique who had been at work only five weeks. He is said to have suffered terrible agony. "He died yelling."

There is no cyanosis or dyspnea; there may be vertigo, and the acute outbreak may be preceded by a period of anorexia, vomiting and diarrhea. Changes in the red blood corpuscles are marked, and the blood of one of the men who died failed entirely to coagulate. It had the color typical of carbon monoxid hemoglobin. In one case the systolic blood pressure dropped from 190 to 112 mm. of mercury in three and a half hours, a fall commensurate with that following a severe hemorrhage. Convalescence is slow, and may take from six to ten weeks.

From the du Pont de Nemours Company's physicians, Eldridge secured a report of the symptoms in twenty-eight cases of tetra-ethyl lead poisoning. The most frequent finding recorded is insomnia (twenty-eight times); then follows a markedly lowered blood pressure (twenty); a subnormal temperature (nineteen); anorexia, nausea and hyperacidity of the urine (eighteen); bodily weakness (sixteen); abdominal cramps (twelve); unaccustomed and annoying dreams (eleven); vertigo and morning vomiting (ten); decided loss of weight (nine), and a slow pulse, increased muscular reactions and headache (seven). Other less frequent findings were a metallic taste in the mouth, tremors, a lead line on the gums (in four cases), and itching of the skin. Lead was detected on the skin of twelve men.

The accidents in New Jersey and Ohio were followed by investigations on the part of the state officials, to determine the extent of the danger in tetra-ethyl lead production and the possibility of protecting workmen against it.

The conditions in Ohio were inspected by H. Ehret of the Factory Inspection Department, and Dr. Nelson C. Dysart. They found that at the time the two fatal accidents occurred, unskilled laborers were employed without skilled supervision, the arrangements for handling the product were crude, the mixing and bottling were carried on under an ordinary laboratory hood, and although the men were given gloves and respirators, they had discarded them. At the time of their visit, however, an excellent building and equipment had been provided as well as working clothes, washing facilities, etc., for the men. "Since the installation of the new filling and blending arrangement with the downward exhaust, no symptoms have been experienced by the workmen, whereas previously complaint of sleepless-

ness, headache, loss of weight and appetite were quite common."

Dr. Andrew McBride, commissioner of labor of the state of New Jersey, made an investigation of the Standard Oil plant and published (Nov. 25, 1924) a report in which he stated that he was opposed "to any attempt to again produce this material by the same processing methods that were used in the past, as experience has demonstrated that workmen cannot be safeguarded against the effects of poisonous contacts." After the first death at Bayway, the other employees who had been exposed to tetra-ethyl lead were taken to the Reconstruction Hospital for observation. Four died a few days later, several exhibited transient symptoms of mental disorder, and one was declared insane, Feb. 18, 1925. The Standard Oil plant was closed after the deaths of the four men in the hospital.

The E. I. du Pont de Nemours & Co. plant at Carney's Point, N. J., where two deaths had previously occurred, was also investigated by Dr. McBride. His report stated that "the danger of exposure was reduced to a minimum," but nevertheless, on Feb. 18, 1925, a man employed in this plant died from exposure to tetra-ethyl lead.

2. *The Danger to Men Handling Ethyl Fluid.*—Ethyl fluid is sold in one quart steel receptacles with pointed necks, sealed with soft tin caps. The service station operator who is to add ethyl fluid to the gasoline in automobile tanks breaks the seal over an upright spike as he places the receptacle over the cup of the delivery tube of the gasoline tank. When the receptacle is empty, he takes it off and substitutes another. There is a recognized danger involved in this process, for the liquid may be splashed over the face and hands of the worker as he jams the receptacle over the opening spike. In view of this fact the manufacturers have stated that in future, sales of tetra-ethyl lead will be made only to refineries, where it will be mixed with gasoline by specially trained employees and then distributed to service stations.[7] This provision, however, is purely voluntary on the part of the manufacturers, and in no state is it a regulation with the force of a law behind it. It is said that small stations which have only one pump cannot buy ready mixed ethyl gasoline, but must add the ethyl fluid to ordinary gasoline on demand.

3. *The Danger to Filling and Distributing Station Employees and to the Public from Handling Ethyl Gasoline.*—A study covering this problem is being conducted at present by the Laboratory of Industrial Hygiene of the Columbia University College of Physicians and Surgeons, New York, and as yet the data collected are insufficient for the formation of a definite statement.

4. *The Danger to Garage Employees and to the Public from Exhaust Gases from Engines Using Ethyl Gasoline.*—The exhaust gases generated by the combustion of ethyl gasoline contain lead compounds in the form of more or less fine dust. The danger here would be from repeated small doses resulting in chronic lead poisoning. The importance of this problem was realized by the General Motors Research Corporation (later the General Motors Chemical Company), and the corporation requested the United States Bureau of Mines to investigate the question. Pending the results of this investigation, the manufacture, distribution and sale of tetra-ethyl lead and of ethyl gasoline were not suspended, but were allowed to continue. The Bureau of Mines began experiments in December, 1923, and just one year later made public a report on Exhaust Gases from Engines Using Ethyl Gasoline. The fact that the report was issued by a government agency gave it an authority and an air of finality, as shown by the fact that immediately after its publication the ban on the manufacture, distribution and sale of ethyl gasoline was lifted by the states of New York[8] and New Jersey, and also by recent articles from the pens of two public officials.[9]

REPORT OF THE BUREAU OF MINES

The experimenters used ordinary motor gasoline, to which was added 3 c.c. of tetra-ethyl lead and 2 c.c. of ethyl dibromid or trichlorethylene, approximately 0.04 and 0.06 per cent., respectively, by volume. The apparatus used was a 1,000 cubic foot air chamber through which air was driven at the rate of 30,000 cubic feet an hour, making a complete change every two minutes. The exhaust gases were generated by a Delco engine and were delivered during the first period through 10 feet of a 1¼ inch pipe; but since a great deal of the lead was deposited in this pipe, a change in the apparatus was made, April 5, and after that the gas was sent in by a 30 inch straight section of pipe and a muffler extending directly from the engine and discharging into the chamber, while the gases were removed by a similar pipe ending near the floor level on the same side of the chamber. As a result, the quantity of lead delivered was increased from 0.5 gm. daily to 1.5 gm. The amount of lead was regulated by the carbon monoxid content of the gas, which was always kept down to the "allowable" limit of 0.4 per thousand, established by Yandell Henderson and his colleagues as the highest permissible for the air in the New York-New Jersey vehicular tunnel.

The animals were placed in cages in the air chamber for three and for six hours daily for varying periods. Twenty-three rabbits, fifteen guinea-pigs, four pigeons, eight dogs and two monkeys were used for the three hour tests; an equal number of rabbits and guinea-pigs, three dogs and four pigeons were given six hour exposures, and at least half as many rabbits, guinea-pigs and pigeons were kept as controls. All were quartered together and given the same amount and kind of food at the same time.

After each running period the deposits in engine hood, exhaust pipe, drip pans and crank case were examined for lead, and it was found that about 63 per cent. of the lead in the gasoline was in these deposits, in the form of sulphate and chlorid or bromid, while the remainder was discharged into the air of the chamber, the larger particles falling to the floor, the lighter remaining suspended in the air. The carbon monoxid content of this air during the second period of the experiment averaged from 0.015 to 0.025 per cent., and the lead, from 0.002 to 0.007 mg. per cubic foot.

Of the animals, 50 per cent. of the rabbits, test and controls, died, and about 25 per cent. of the exposed guinea-pigs; nine of the ten dogs survived, and also the two monkeys and the pigeons. All deaths are attributed to accident or disease, mostly of an infectious nature. No loss of weight was noted, no anemia, no lead lines, no evidence of lead poisoning either

7. Shrader, J. H.: Tetra-Ethyl Lead and the Public Health, Am. J. Pub. Health 15: 213, 1925.

8. At Albany, Jan. 20, 1925, on the advice of the Public Health Council of New York State.

9. Shrader (Footnote 7). Sails, C. M.: The Nation's Health, New York State Dept. of Labor 7: 169 (March 15) 1925.

through symptoms or from analysis of feces. Examination of the blood of six three-hour rabbits, four six-hour rabbits and two dogs showed no stippling of the red cells, only a slight polychromatophilia, anisocytosis and poikilocytosis. The blood of the guinea pigs showed stippling, but no more in the test animals than in the controls.

The carcasses of seven guinea-pigs, one dog and eleven rabbits were examined for lead by Fairhall's [10] method, and very insignificant amounts were found, the largest being 0.33 mg. per hundred grams of body weight. Lead was found in controls as well as in test animals. The authors conclude that this shows that latent or delayed poisoning is not a possibility under these circumstances, since no storage of lead took place.

To estimate the danger from the quantity of lead found in the exhaust gases, an experiment in inhalation and exhalation was made. Six men breathed these gases through a specially designed mask with double acting valves which collected the exhaled air. It was found that of the lead inhaled, only from 8 to 27 per cent. was retained, an average of 15 per cent. From this the authors reason that the quantities of lead found in the air of the test chamber are negligible and that "the only danger of lead poisoning from products of combustion of ethyl gasoline seems to be confined possibly to the mechanic who is continually cleaning carbon from motors." This risk they believe to be no greater than that incurred by painters.

CRITICAL REVIEW OF THE REPORT BY DRINKER AND EDSALL

A review of this report by Drinker and Edsall [11] of Harvard has appeared. These reviewers believe that the report loses a truly convincing character because of the small number of animals that actually went through the test. The mortality of both test and control animals was excessive (50 per cent. of rabbits, 25 per cent. of the guinea-pigs), and this lessens the value of the experiments. All these deaths are taken as due to infections or accidents of various sorts, and are said to have been as frequent in control animals as in experimental; but "it is unfortunate that better experimental stock was not available for experiments of this degree of importance." They question the adequacy of the data on which the authors base their assertion that a man breathing the exhaust from an engine retains only 15 per cent. of the lead inhaled, and they are unwilling to apply these results to animals without direct experiments on the species in question. The material is, in their view, presented in too insufficient detail. No data are given as to the size, composition or settling of lead in the air delivered to the test chamber, the lead being assumed to be in the form of particulate matter, not a gas. It seems to them an unwarranted assertion that such particles would pass out of the air of a garage in the same manner as would the exhaust gases from gasoline engines. For this reason and because the amount of lead was kept extraordinarily low in the air of the test chamber, it cannot be assumed that these conditions imitated the actual circumstances under which the public must meet the combustion products of ethyl gasoline. What the experiments do show is that "with a ventilation system which prevents the atmospheric lead delivered to the air by engines using ethyl gasoline from attaining more than 0.002 to 0.007 mg. of lead per cubic foot, a condition results which, in a limited number of animals, has been demonstrated to be safe."

To these criticisms we would add the following:

CHANGE IN METHOD OF CONDUCTING EXPERIMENT AT END OF FIRST FOUR MONTHS

From the start of the experiment, Dec. 6, 1923, to April 2, 1924, which covers one half of the time of the reported study, the air delivered into the experimental chamber contained an average of only 0.00043 mg. of lead per cubic foot (tests for lead averaged up to April 2), but for the last four months of the experiment the lead in the air was increased to 0.0045 mg. per cubic foot (tests for lead averaged from April 2 to July 22). Moreover, the ventilating system used during the first four months of study appeared to the investigators to be unsatisfactory, and on April 23 a change was made. Under the new system the exhaust gases were conveyed to the chamber through a 10-inch pipe and removed from the chamber by means of a similar pipe opening near the floor level on the same side of the chamber. Such an arrangement might well produce a short-circuiting of the air which would interfere seriously with the general ventilation of the chamber.

Since two entirely different methods of ventilating the experimental chamber were used, it would appear that the first four months of the experiment were of little value and that the results from the two methods should not be added together or averaged together.

LENGTH OF EXPOSURE OF ANIMALS

A cursory reading of the report conveys the impression that some ninety-seven animals were exposed to the fumes from ethyl gasoline engines for a period lasting from December 6 to July 22, but a more careful study shows that, owing largely to the mortality among the animals, the actual period of exposure was much shorter. Blood pictures are given for only twelve of the test animals, and of these, nine were exposed for three months or less; viz., eight for three months, one for two months, and three for five and a half months. Reports on tissues analyzed for lead are given in only nineteen of ninety-seven exposed animals, and more than half of these (ten out of nineteen) were exposed to ethyl gasoline for only three months or less. Six animals were exposed for three weeks or less; four for from three weeks to three months; six for from three to five months, and three for more than five months.

CONTROL ANIMALS WERE NOT EXPOSED TO CARBON MONOXID

The animals in the experiment chamber were exposed to two poisons, carbon monoxid, and lead, the controls to neither. Since it has been established by Nasmith and Graham [12] that exposure to small doses of carbon monoxid for successive days produces in experimental animals an increased red blood cell count, some doubt must be cast on the records of blood counts in the test animals. The tables show that there was no decrease in erythrocytes in the test animals, and the conclusion is drawn that these animals showed no lead anemia. To prove this point, the effect of repeated exposures to carbon monoxid would have to be tested on control animals. As a matter of fact, direct examination of smears did show some polychromatophilia, anisocytosis and poikilocytosis, all evidences of secondary anemia.

10. Fairhall, L. T.: The Estimation of Minute Amounts of Lead in Biological Material, J. Indust. Hyg. 4: 20 (May) 1922.

11. Drinker, C. K., and Edsall, D. L.: J. Indust. Hyg. 7: 94 (Feb.) 1925.

12. Nasmith, G. G., and Graham, D. [illegible] Hematology of Carbon Monoxid Poisoning, J. Physiol. 7: 35.

CONTROL AND TEST ANIMALS WERE QUARTERED TOGETHER

The Bureau of Mines report states that "all animals were quartered together and given the same amount and kind of food at the same feeding time." This procedure is open to criticism, since the excretions of animals exposed to lead would affect the control animals, and this may account for the fact that lead was found in the tissues of the control animals, for normal tissues should show no lead. For the same reason, the three-hour animals should not have been quartered with the six-hour animals.

CHARACTER OF DIET NOT STATED

No statement is made regarding the food given the animals, and yet diet and exposure to sunlight have a direct influence on the fate of ingested lead and may determine whether it shall be stored in temporary harmlessness or circulated or excreted. If animals exposed to lead are put on a high calcium diet (milk) and placed in direct sunlight, they can accumulate large amounts of lead and show neither signs nor symptoms of lead poisoning.

ANALYSIS OF EXCRETIONS

No analyses of excretions were made, and yet examination of stools for lead gives important evidence as to the amount of lead passing through the body. It would also have been important to know in which tissues the lead was found in the animals that were killed. This would have shown whether the lead was being stored in comparative safety in the skeleton or whether it was actually in circulation.

INTERPRETATION OF SYMPTOMS IN ANIMALS

There is some confusion in the report with regard to the condition of the experimental animals. In the protocols, we find that one animal was emaciated before death and that one dog and one rabbit were paralyzed before death, but in the summary the statement is made that none of the animals lost weight or were paralyzed. This discrepancy between observations and conclusions is not explained. It is reported that none of the animals had colic, but colic is difficult to determine in animals and its absence can only be surmised.

The statement is made with regard to a dog that was killed after paralysis had set in that "no stippling or lead line was found." Dogs poisoned by lead probably do not show stippled red cells.[13] The comment, "no lead line," was made in regard to rabbits which died, but in rabbits lead poisoning is not accompanied by the formation of a lead line, which occurs in few animals, notably in cats, never in rabbits. Whether dogs poisoned with lead show a lead line is as yet not known. The cause of paralysis and emaciation in the experimental animals is not sufficiently explained, and with regard to the monkeys very few facts are given, no records of weight, blood findings, lead line or analysis of stool or urine.

QUANTITY OF EXHAUST GAS IN TEST ROOM NOT TYPICAL OF ACTUAL CONDITIONS

The animals under test were kept in an atmosphere containing exhaust gases up to a concentration of 4 parts of carbon monoxid in 10,000. This limit was set because it is the amount of carbon monoxid set by Yandell Henderson and his associates as the highest limit to be allowed in the air in the New York-New Jersey vehicular tunnel. The investigators refer repeatedly to this standard as the "permissible" or "allowable" amount of carbon monoxid. In a personal communication, Henderson makes this comment:

> It is indeed the highest amount that should, on grounds of healthfulness, exist at any time in a garage; but there is ample evidence in our investigations and, particularly, also, in the recent report by Dr. Ettore Ciampolini of the New York Department of Labor, in his study of public garages, to show that the atmosphere in such places is often contaminated to a far greater extent than the 4 to 10,000. At present with the form of exhaust used on most automobiles it is quite impossible to keep the air of garages to a healthful standard in regard to carbon monoxid. For the same reason, garage workers, even on the basis of the Bureau of Mines report, will be exposed to several times as much lead dust as were the animals reported in those experiments. Moreover, in the test room the rapid artificial ventilation prevented the lead from accumulating as dust as it does in a garage or on the streets. It would have been a nearer approach to real conditions if the exhaust gas had been blown through the chamber for several weeks without putting any animals into the chamber. Then, when an amount of dust had collected corresponding to that which occurs in a garage, the exhaust could have been shut off, and the animals could then have been made to live in this dusty room for a few weeks. An experiment of that sort would have approximated real conditions in a garage.

NEGATIVE RESULTS AS TO LEAD POISONING

The period of exposure of the animals was too short and the method used was not such as to produce convincing results. It is notoriously difficult to bring about lead poisoning in animals by the respiratory route unless an extraordinary measure is used, such as insufflation of lead dust, because the upper respiratory tract in these animals is very well protected. Such experiments can hardly be accepted as solving the problem for human beings.

The conclusion drawn in the report that "the only danger of lead poisoning from products of combustion from ethyl gasoline seems to be confined possibly to the mechanic who is continually cleaning carbon from motors" is apparently based on the large proportion of lead which was deposited in the engine pipe, etc., and on the inhalation experiments, which showed that only 15 per cent. of the inhaled lead remains within the body.

CONCLUSIONS

We believe that these conclusions are not warranted and that the evidence so far available seems to show a real danger of chronic lead poisoning connected with garage work when ethyl gasoline is used and a possible danger to the public from lead dust in the streets of large cities. The compounds of lead formed by the combustion of ethyl gasoline are the chlorid or bromid, according to the carrier used, and the sulphate. A quantitative analysis made by the Bureau of Mines' investigators of the deposits in engine head, exhaust pipe, crank case, and drip pan under the exhaust outlet, showed that 95.2 per cent. of the deposit consisted of lead, of which 40.1 per cent. was in the form of chlorid or bromid, and 55.1 per cent. in the form of sulphate (p. 9). Now, the chlorid and bromid of lead are among the most soluble of the lead salts, far more

Solubility in Grams per Liter of Water

Lead, basic carbonate (white lead)	0.0016
Lead oxids (red lead, litharge, etc.)	0.02
Lead sulphate	0.041
Lead bromid	8.3
Lead chlorid	9.6

13. Aub, J. C.; Reznikoff, Paul; and Smith, D. E.: Lead Studies, III, The Effect of Lead on Red Blood Cells, J. Exper. Med. **40**: 151 (Aug.) 1924.

soluble in water than are those usually encountered in industry, as can be seen by the accompanying table."

The statement, therefore, that only 15 per cent. of the inhaled lead is retained is not entirely reassuring, even if one accepts it as proved. A finely divided soluble lead compound can be readily absorbed from the respiratory tract, beginning with the nasal mucosa,[15] and may constitute a serious danger if administered in repeated doses, even if these are small.

It seems to us that the investigators have devoted their attention to the fine particles of lead suspended in the air and have not attributed enough importance to the discharge of "large particles of scale which fall to the ground," and which, in garages, in taxi stands under cover in the large railway stations, and even on the crowded streets of cities, might constitute a far from negligible danger. These particles will be ground fine by passing feet and swept up by currents of air, and when dissolved by rain and washed away, it is certainly possible that they may contaminate surface waters. It is also well to remember that when tetra-ethyl lead was first used in motor gasoline, all the lead was deposited in the engine, and it was for this reason that a halogen carrier was added, in order to get some of the lead out of the engine. Later improvements will probably result in further progress in this direction and an increase in the amount of lead discharged into the air.

SUMMARY

Tetra-ethyl lead is added to gasoline together with a volatile "carrier," ethylene dibromid or trichlorethylene, to prevent "knocking" in motor engines.

Experiments carried on by Eldridge of the Chemical Warfare Service show that tetra-ethyl lead passes readily through the skin and that rapid acute poisoning may follow skin application or the inhalation of fumes. In animals so poisoned, the lead is found deposited chiefly in the skeleton. A cumulative effect also was noted, when animals were given repeated small doses by these two routes, death occurring in more than half.

The production of tetra-ethyl lead for commercial purposes resulted in the poisoning of some sixty or seventy men and the death of ten men, in a period of thirteen months, ending Nov. 1, 1924. Since then great improvements in equipment have been made, and only two serious cases of poisoning have been reported during 1925. One man died, and one was declared insane in February, 1925.

The mixing of ethyl fluid with gasoline constitutes a danger, the extent of which is as yet undetermined, to employees of refineries and service station employees.

The use of gasoline to which ethyl fluid has been added constitutes a probable risk to garage workers and a possible risk to the public, of chronic lead poisoning, because the combustion of tetra-ethyl gasoline results in the formation of soluble compounds of lead, the chlorid and bromid (as well as the less soluble sulphate), which compounds pass out with the exhaust gases in the form of light and heavy particles.

The states of New York and New Jersey prohibited for a time the use of ethyl gasoline, but rescinded this order when a report was issued by the United States Bureau of Mines declaring that tests made on animals with exhaust gases from engines using ethyl gasoline had shown no evidence of plumbism in any of these animals.

This report of the Bureau of Mines has been critically examined and found to be inadequate in scope, in technic, and in conclusiveness. It cannot be accepted as the final word on the question as to the toxicity of exhaust gases from cars using ethyl gasoline. The further question, of the risk to garage workers, is only lightly touched on in this report, and it also must await a more thorough handling.

Because of the enormous and increasing use of automobiles, the question of the danger to industrial workers and to the public which is involved in the production and handling of tetra-ethyl lead and the use of ethyl gasoline is of the highest importance and calls for a study which will be beyond criticism. Such an investigation must include an intensive survey of a selected group of individuals who have already been exposed to the gas, under known and varying calcium diet and varying exposure to sunlight. Their excreta should be analyzed for lead. Only in this way can absorption of lead and possible lead poisoning be ruled out. Perhaps of even greater significance is the possibility that the gonads may be injured and posterity be affected,[16] even without any marked effect on the individual. This would necessitate studying the progeny of pedigreed animals. Until investigations of this character have been made, it would seem to be in the interest of public health to suspend the use of tetra-ethyl lead in gasoline.

14. Personal communication to the authors from Prof. Julius Stieglitz, Department of Chemistry, University of Chicago.

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PARATHYROID TETANY

REPORT OF A SEVERE CASE TREATED WITH MASSIVE DOSES OF CALCIUM LACTATE *

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Almost since the beginning of thyroid surgery, a postoperative condition of tetany has been noted. This was at first ascribed to thyroid deficiency, but animal experimentation clearly differentiated the process and proved it dependent on parathyroid deficiency, a fact subsequently substantiated clinically in numerous instances.

The condition probably will increase rather than decrease, owing, as one chief of a prominent clinic remarked, "to the necessity of removing more thyroid in order to secure a greater degree of cure." [1]

The treatment of this condition has always been a matter of grave concern. Parathyroid transplantation, desiccated gland orally, extracts of the gland subcutaneously and intravenously, and various salts by mouth, by rectum and intravenously have been tried, but usually without success in the severe cases.

Frouin [2] was one of the first to call attention to the oral efficacy of calcium and magnesium salts in parathyreidectomized dogs. Luckhardt and his co-workers [3]

* From the surgical service of John E. Jennings, the Brooklyn Hospital.

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