EXPERIMENTAL STUDIES

ON

TETRAETHYL LEAD POISONING

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THE TOXICITY OF TETRAETHYL LEAD.

The toxicity of tetraethyl lead for rabbits has been determined for the various methods of administration, and it has been compared with the toxicity of certain inorganic salts of lead. In the case of both tetraethyl lead and the inorganic salts of lead a sufficient number of animals have been studied to make possible a proper allowance for individual variation. If only the lethal amount for a single administration be considered, little individual variation is seen. However, if the toxicity be considered on the basis of numerous repeated administrations, a considerable variation is found.

The fatal dosages of tetraethyl lead administered in one dose to rabbits by various means are substantially as follows: Intravenously, 0.014 cc. per kilo body weight, approximately 0.014 grams lead per kilo; cutaneously 0.7 cc. per kilo body weight, or about 0.7 grams lead per kilo; by oral administration 0.11 c.c. per kilo body weight or about 0.11 grams lead per kilo; the quantity taken into the body of the animal by inhalation is difficult to calculate for a variety of reasons, but the concentration of tetraethyl lead in terms of lead in the air breathed by the animal which will kill in about three days of six-hour daily exposure is approximately 0.182 mg. per liter of air.

In all of these methods death of the animal takes place in from six to seventy-two hours.

The fatal dosages of salts of lead such as the chloride and nitrate are not widely variant from the above figures.

When lead chloride is administered intravanously, a variety of things may occur, dependent upon the salt employed, the speed of administration and the concentration of the solution. The animal may die at once; he may develop a thrombosis at the site of the injection, or he may develop a general systemic poisoning. The lethal dosage is calculated on the basis of the last situation, to be about 0.015 grams of lead per kilo.

When administered orally, approximately 0.037 grams of lead per kilo are required to produce death from one dose.

In the case of lead nitrate approximately 0.011 grams of lead per kilo injected intravenously brings about death within twenty-four hours.

The cutaneous application of inorganic salts of lead results neither in death nor illness of the animals.

Comparison of the toxicity of tetraethyl lead with that of the inorganic salts of lead, shows that in general these are of the same order of magnitude. An exception of sufficient magnitude to be well outside the limit of chance variation is seen, however, when one compares the poisonous character of lead salts taken by mouth with that of tetraethyl lead taken in the same way. In this case the salts of lead are seen to

be about three times as toxic as tetraethyl lead. This is probably due to the greater ease of absorption of lead salts in the alimentary tract. On the other hand, lead salts are not absorbed in lethal doses from skin, whereas death may readily be produced by the application of tetraethyl lead to the skin.

The general conclusion which seems to be obvious from the above data, is that tetraethyl lead owes its toxicity to the lead and not to any other part of the compound, tetraethyl lead, is not peculiarly toxic as compared with other heavy metal compounds, but that its principal danger resides in the fact that it is readily absorbed through the skin, as well as being capable of inhalation because of its volatility.

When tetraethyl lead is administered in smaller repeated doses, the outcome is dependent upon the size of the dose and the time interval between doses. In a series of rabbits treated with 0.1 c.c. at intervals of three days symptoms began to appear in most cases after six to eight treatments. (The only symptom was a slight loss of weight.) The total quantity applied before the death of these animals averaged about twice the amount of a single lethal dose. It will be seen from the consideration of later experiments that the lethal amount is dependent not so much on the total quantity of lead which the animal is led to absorb, but rather upon the concentration actively mobilized (in the blood stream probably) at a particular time.

THE ACCUMULATION OF LEAD IN EXPERIMENTAL ANIMALS TREATED WITH TETRAETHYL LEAD

When rabbits are treated at regular intervals with sub-lethal doses of tetraethyl lead, there is an accumulation of lead in the body of the animal. The rate of accumulation depends upon the size of the dose administered and the time interval between injections. The quantity of lead found in the animal varies, however, not only with the quantity administered, but also with the time which has elapsed between administration of the last dose and the time of analysis of the animal.

That is, the rate of secretion is of such an order of magnitude as to make striking differences in the quantity of lead found in animals treated in an identical manner.

With the accummulation of lead in the animal there is no evidence of a chronic poisoning, with the single exception of a slight loss of weight. If the animal becomes ill, his symptoms are acute and death results.

In the table below may be seen observations and analytical data collected on a series of nine rabbits, treated at intervals of three days with 0.1 c.c. of pure tetraethyl lead, applied to the skin of the abdomen.

Rabbit	Weight	Number of Treatments	Time of Appearance of loss of weight.	Result	Lead Determination in milligrams
No. 31	5-3/8 #	16	7th treatment	Died 23 days after last treatment.	15.3
No. 34	6-1/8 #	13	No loss of weight	Same	9.78
No. 35	6 #	15	8th treatment	Died day after 15th treatment	96.0
No. 36	5-3/4 #	17	14th "	Survived	
No. 37	6-3/4 #	7		Died after 7th treatment	90.
No. 39	4-7/8 #	14	7th "	Died 29 days after last treatment	7.10
No. 40	4-1/2 #	14	7th "	Survived	
No. 42	4-5/8 #	11	9th "	Died after 11th treatment	51.25
No. 60	3-1/2 #	10	7th "	Survived	

That the large variations in the quantity of lead found in these animals may be, and probably are due to the secretion of lead by the animal is indicatod by the data collected on the rate of secretion of lead from the body of certain of these animals.

The animals in this case were installed in the ordinary metabolism cage with a lead free floor. The urine and faeces were collected over periods of several days and analysis was made. The cages were first tested as to their lead-free character by using lead-free animals as controls. The diets of the animals were unchanged during the period of collection.

Rabbit	Period of Collection	Quantity of Lead in Milligrams
2 controls	7 days	Nil
No. 31*	7 "	5.89
No. 36	7 "	4.00
No. 39	7 "	2.08

* Note: This animal died December 21. His entire body contained 15.3 mg. lead. Some idea can be obtained of the quantity of lead in the body of this animal at a time when he was excreting almost 1 mg. per day.

This fairly rapid rate of excretion raises the question as to whether in the decomposition of the tetraethyl lead molecule a compound of lead may not be formed which is more readily excreted than the ordinary compounds of lead. This question is presented the more strongly when the rate of excretion of lead in men poisoned by tetraethyl lead is studied.

THE DISTRIBUTION OF LEAD IN POISONED ANIMALS.

A number of animals known to contain considerable quantities of lead at the time of death were analyzed after the separation of their tissues. The data below indicates the manner of poisoning of the animal, together with the lead content of various tissues.

Rabbit No. 32 - Exposed for 72 days to vapor of Pb $(Et)_4$ in air at the rate of 100 cc. $Pb(Et)_4$ vapor to 5 liters of air.

Tissue	Weight	Lead in Milligrams
Bones	225 grams	9.15
Skin	300 "	3.18
Liver and Kidneys	56 "	3.70
Central Nervous System	13 "	Nil
Fetuses in Utero	126 "	0.28
Other tissue	2045 "	8.75

Note: One liter of saturated vapor of $Pb(Et)_4$ at 25° C. contains 0.00456 grams Pb.

Rabbit No. 31 - Treated every three days with 0.1 cc. $Pb(Et)_4$, sixteen treatments. Died twenty-three days after last treatment.

Tissue	Weight	Lead in Milligrams
Bones	325 grams	8.04
Skin	260 "	4.49
Liver and Kidneys	105 "	1.15
Central Nervous System	13.5 "	Lost in analysis
Other tissue	1590 "	2.02
Urine in Bladder	50 c.c.	0.14

Rabbit No. 16 - Exposed for ninety-dight days to vapor of $Pb(Et)_4$ in air at rate of 5 cc. of $Pb(Et)_4$ vapor to 5 liters of air, and then for three days to 200 cc. vapor in five liters of air. Died.

Tissue	Weight	Lead in Milligrams
Bones	520 grams	2.22
Liver	82 "	3.75
Central Nervous System	18 "	0.13
Remainder (without skin)	2160 "	26.00

THE EFFECT OF TETRAETHYL LEAD ON ANIMALS

When toxic amounts of tetraethyl lead are administered to rabbits, the first symptoms seen are lack of appetite and loss of weight. A sluggishness and lassitude are apparent, and the animal sits with drooped ears and arched back. As the symptoms increase in severity, he becomes nervous, moving about in the cage from place to place, stopping from time to time to sink into a drowsy state. The temperature does not ordinarily vary more than is normal in these animals, but respiration quickens at first and then, with increasing severity of symptoms, decreases. If sufficient time intervenes before death, a watery diarrhoea develops. Convulsions usually occur as a terminal sign, and the animal dies with bulging, congested eyes and paralyzed respiration, with the heart continuing for some time afterward. When illness results from inhalation there is an irritation, with some weeping of the mucous membranes. The upper respiratory tract may become red and in very severe cases even haemorrhagic. When the application is made on the abdominal wall, there is an almost immediate increase in the peristaltic activity of the intestimes. Rapid peristalsis may be easily observed under the abdominal wall. During the course of their illness, whether acute or prolonged, no characteristic objective signs develop. There is no typical alteration of the blood picture. (Stippling and polychromatophilia are found almost uniformly in normal rabbits, so that no minute changes

would be demonstrable.) Only a slight anemia has appeared in any experimental animal thus far.

Post-mortem examination of poisoned animals discloses certain characteristic, though not definitely differentiating, changes. These are confined almost wholly to the alimentary tract and the central nervous system. There is a considerable amount of capillary dilitation of the viscera generally and the heart is usually dilated and flabby, but the pronounced findings are seen in an acute intestinal irritation and desquamation and an acute edema of the brain. The intestinal change is confined almost wholly to the small intestine and is most pronounced in the duodenum. Here the intestine is filled with a sticky mucoid fluid which may be, but usually is not, blood tinged. It is characteristically yellowish and glairy, and often coggulates spontaneously on standing for a time. The mucosa in this region is thin and almost fluid in character. No actual ulceration is found, and there are seldom any definite haemorrhagic areas. The brain is either dry and swollen and very friable, or else it is very wet with a large amount of free fluid under the dura, especially at the base.

Microscopic findings are very meager. No characteristic change has been found. The study of microscopic pathology has not been completed.

Among the effects on experimental animals, which should be noted in passing is the influence of lead poisoning on pregnancy and the procreative functions in general. A number of pregnant female rabbits have given birth to premature litters. In several cases abortion or miscarriage has resulted shortly after the administration of the poison. However, the loss of ability to reproduce has not occurred in the case of either male or female rabbits. Animals which have been severely poisoned have both fertilized and become impregnated and have brought forth normal young after only brief periods of recovery.

ON THE ABSORPTION OF TETRAETHYL LEAD THROUGH THE SKIN,

AND

THE ABSORPTION OF TETRAETHYL LEAD OUT OF GASOLINE.

In the former experiments, in which the toxicity of tetraethyl lead as absorbed through the skin, was determined, there was in almost egery case a possibility that the animal had obtained a portion of the lead by inhalation and ingestion. It was determined, therefore, to carry out some experiments to control this factor, and to establish, beyond any doubt, the facts in the matter. Accordingly, animals were selected of approximately the same size and age and were exposed to a definite concentration of tetraethyl lead in gasoline for a definite period of time, after which the tetraethyl lead was carefully removed by means of kerosene, and subsequently soap and water. During the period of exposure the animal was tied down, and ventilation was maintained in such a way as to prevent appreciable inhalation of the gasoline-tetraethyl lead vapor. A second purpose in these experiments was to discover whether tetraethyl lead could be absorbed through the skin out of gasoline. The practical importance of the latter question lay in the fact that the exposure to tetraethyl lead, on the part of distributors and consumers, would have to do with this solution in contact with the skin. Since in almost every case such gascline would be wiped off or washed off before evaporation, the relative rates of absorption of gasoline and tetraethyl lead, and the partition occurring between the gasoline and the skin, as solvents for tetraethyl lead, would determine, largely the magnitude of any hazard arising from exposure to gasoline containing tetraethyl lead.

The following experiments show that tetraethyl lead may be absorbed through the skin of experimental animals, in quantities sufficient to produce death, when the factors of inhalation and ingestion are adequately controlled. Further, they show, that thetraethyl lead may be absorbed out of gasoline, though there is no indication of any selective absorption. They indicate, however, that the quantity of tetraethyl lead which may be absorbed out of a solution of tetraethyl lead in gasoline comparable to commercial "Ethyl Gasoline", is very minute.

Experiments.

1. Three rabbits of approximately the same weight (about 2 kilo) were exposed for half an hour each, on three consecutive days, to a one to ten dilution of tetraethyl lead in gasoline. Each animal was carefully tied down on a comfortable board, as much as possible of the hair was clipped from a fore leg without any abrasion, and the leg was gently but firmly held in a test tube of the solution, down to the elbow joint. Care was taken not to interfere with the circulation. The quantity of solution to which the leg was exposed was approximately 35 cc. The exposure was carried out in a hood where the air was being changed rapidly. At the end of the exposure the leg was bathed in kerosene repeatedly, wiped dry, and then treated with cold cream, for the purpose of counteracting the harmful effect of the gasoline on the skin.

At the end of three such treatments, the animals developed paralysis of the hind legs, and on the next day they died. Control animals, two in number, of the same weight, treated in exactly the same manner,

except that the gasoline contained no tetraethyl lead, showed no indication of injury beyond some degree of irritation of the skin.

One of the animals was ashed and an analysis for lead was made. The entire carcass contained 36.46 milligrams of lead. It is well to point out that this animal had been exposed for 1-1/2 hours to 105 cc. of a solution containing approximately 10 grams of lead. Approximately 0.35 of 1% was absorbed.

2. Ten rabbits were selected and were treated in the same manner, three being used as controls, and seven being exposed for half an hour at a time to a dilution of one part of tetraethyl lead in one hundred parts of gasoline. For the first seven days the treatment was carried out daily. After this the exposureswere made twice weekly. This was done because of the skin irritation which resulted from the daily treatment. It was found that the skin could be kept intact by increasing the interval between exposures, provided the skin be treated with cold cream in the interval.

The following table shows the results of such treatment:

No. Animal	No. Treatments	Weight Before	Weight After	Result
89 control	28	2-3/4	5-1/8	Survived
93 "	27	4-1/4	5-1/8	"
98 "	27	3-1/4	3-3/4	"
90 1:100	7	4-1/4	4-3/8	Killed for analysis*
91 1:100	29	3-3/4	4-3/4	Survived
92 1:100	29	4-3/4	5-1/8	"

No.	Animal	No. Treatments	Weight Before	Weight After	Result
94	1:100	16	4-1/4	4-1/2	Died suddenly without previous illness**
95	1:100	27	4-1/4	3-1/2	Ill after 10th treatment. Recovered.
96	1:100	25	5-1/4	6-1/2	Survived.
97	1:100	22	4	4-1/2	Paralysis and death***

* Lead content of carcass of 90 3.81 mg.

** Lead content of carcass of 94 7.50 mg.

*** No analysis was made of carcass of 97.

The above data show that there is an accumulation of lead in rabbits treated with gasoline containing a sufficient quantity of tetraethyl lead, and that the animals may be poisoned by a concentration of one part tetraethyl lead to one hundred parts of gasoline. It is of some importance to see that animals treated with a concentration of one part of tetraethyl lead to one hundred parts of gasoline absorbed approximately one-thirtieth as much as animals exposed under identical conditions to ten times that concentration, i.e. one to ten.

ON THE TOXICITY OF ETHYL GASOLINE.

The question of the hazard existing in the handling of Ethyl Gasoline hinges upon two considerations:

(a) whether the quantity of tetraethyl lead volatilizing out of gasoline at the existing concentration (1.1300 approximately) is sufficient to cause appreciable absorption of lead;

(b) whether skin absorption of tetraethyl lead in gasoline can occur to an extent sufficient to cause poisoning.

Note: From the Research Laboratories of the Ethyl Gasoline Corporation and the Eichberg Laboratory of Physiology, University of Cincinnati, Cincinnati, Ohio.

Both of these problems were investigated by exposing animals to conditions as nearly like the normal conditions of human exposure as could be devised. For this purpose guinea pigs and monkeys were selected; guinea pigs, because of their susceptibility to lead poisoning, and monkeys because of their similarity to the human being.

The guinea pigs were divided into four groups, kept separate, but fed and cared for in exactly the same manner. Eleven pigs, four females and the remainder males, were treated on the skin surface of the belly, after clipping off the hair, with 1 cc. of ethylized gasoline. Eleven, all females, were set aside as untreated controls. Eleven, five of which were females, were treated with 0.2 cc. of ethylized gasoline. Three, one male and two females, were treated with 1 cc. of ordinary gasoline.

The gasoline used was a good grade of high test commercial gasoline. The ethylized gasoline was prepared by first making a mixture of pure tetraethyl lead and ethylene dibromide in the proportion of three parts of lead to two parts of dibromide. This mixture was kept in a tightly sealed brown bottle to prevent decomposition, and was mixed in gasoline in quantities of 0.25 cc. to 200 cc. of gasoline, as needed. This corresponds to the most concentrated mixture of tetraethyl lead in gasoline, known as a 3 E. mix., representing approximately one part by volume of tetraethyl lead per thirteen hundred parts of gasoline.

The monkeys, four in number, of the Rhesus type, were all cared for in the same manner. Two were used for controls, and two were treated daily with 2 cc. of Ethyl gasoline, prepared in the above manner.

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The hair was clipped from an area on the back, as large as the palm of the hand and the gasoline mixture was dropped on out of a pipette. One of the monkeys to be used as a control died within a few days after his arrival, having contracted pneumonia in transit. The other control escaped from his cage and died of exposure before he could be captured. The two being treated as above were continued without any controls for comparison.

The following paragraphs indicate the course of the experiments carried out upon these animals.

GUINEA PIGS.

Pen No. 1.	4 females 7 males treatments twice weekly.	Treated with 1 cc. Ethyl Gasoline. Number of treatments 40.

In the period from November 25th, to the present there have been no natural deaths among these animals. Three were killed for analysis on March 3rd, and one was killed for analysis on March 31. The females have given birth to six young which have survived, two of which were born May 14th. There have been two litters of young born dead. These occurred in January and February, during periods of inclement weather, in which all of the animals suffered somewhat.

Two pigs were selected, because of distinctive markings, for observation of blood conditions. The initial observations on the two were as follows:

(a) Hb. (Dare Method) 90, Red Count, 6,160,000

(b) Hb. 110, " " 5,200,000

Observations made on May 17th, were as follows:

(a) Hb. 90 Red Count, 5,754,000

(b) Hb. 105, " " 5,230,000

Blood smears show no appreciable change now as compared with the original observations. Guinea pig blood under normal conditions shows a variable amount of polychromatophilia, and an occasional stippled cell may be found in the blood of a normal animal. In the two pigs above no stippling has ever been seen. Bluish or basophilic staining erythrocytes may be seen in almost every field. There has been no noticeable increase in the number of these.

Of the 7 pigs remaining in this group two males do not appear to be in good condition at present. They have been fighting almost constantly lately, and have inflicted many deep wounds upon each other, some of which are infected and suppurating. It has been thought advisable to segregate these animals and continue the experiment to see if healing of wounds will bring about recovery. The two females remaining look healthy and sleek, except for the irritation of the skin of the belly.

Pen No. 2. 11 Females. Not treated. Male from Pen 4 introduced.

There have been no natural deaths among these animals. Three were killed for analysis, March 3rd, and one was killed for analysis March 31st. Forty young have been born alive, of which three have died within a few days of the day of their birth. Three females have given birth prematurely to young, one of these on May 13th.

Two pigs were selected for their distinctive markings, and blood examinations were made as in the case of group No. 1. No variation was seen in the blood picture, and no variation as compared with those in Pen No. 1 was seen, except that in one pig an occasional stippled erythrocyte was found.

These animals are in good condition, and present no demonstrable deviation from the normal.

Pen. No. 3.	6 Females 5 Males Treatments twice weekly.	Treated with 0.2 cc. Ethyl Gasoline. Number of treatments 40.

Since November 25th, the beginning of the experiment, there have been no deaths among these animals as a result of illness. Three were killed for analysis on March 3rd. Twenty-four young ones have been born, of which nineteen are now alive. The others died within a day or two of their birth. There have been three litters born dead. None of these occurred since April 1st.

The blood findings in these animals are no more significant than those in the other groups of pigs. No variation from the normal has been found in spite of repeated examinations.

The animals are all healthy.

Pen No. 4.	1 Male 2 Females Treatments twice weekly.	Treated with 1 cc. Gasoline. Number of treatments 40

There have been no deaths in this group. Two litters of young have been born, six young in all, of which one was dead at birth.

No blood examinations have been made on the pigs in this pen

since the first examination. They were used largely as controls on the influence of the gasoline alone on the skin. No variation is seen either in the condition of their skin, or their general appearance as compared to treated animals.

An unfortunate and unforeseen variable was found in the conduct of these experiments, when a group of treated and control animals were killed for analysis on March 3rd. The table below shows the lead content of the carcasses of these animals. It will be seen that the quantity of lead is practically the same in all animals, treated and control alike. This was not due to any mistakes in handling or treating the animals, nor was there the remotest chance of incorrect selection of animals for analysis. The explanation can be found only in a detailed consideration of all the environmental factors. The first three groups of these animals were quartered in a single large pen, divided into three parts by wooden partitions of tongued and grooved siding. The top and front side were made of inch mesh wire netting. There was no chance, therefore, for the excreta of one group of animals contaminating the food of the others; nor could dust from one cage enter the other in considerable quantity.

When the animals were treated, they were kept on the
al board until the treated surface was dry, before being returned to
cages. No special ventilation was employed, since there was no ob-
ion in this case to inhalation of gasoline and tetraethyl lead vapor.
the case of human exposure, both of these possibilities are presented).
r these conditions, the opportunity for inhalation of vapor from treated
als was not presented to control animals.

The cause for the experimental result can be found only in a condition to which all of the animals were equally exposed. One end of the large room, which was being used for housing the animals during the cold weather, was used from time to time as a place of storage for returned packing cases filled with empty and full cans used for the early distribution of tetraethyl lead.

It is apparent, and should have been foreseen, that a quantity of the dust resultant from the decomposition of such a portion of tetraethyl lead as was left in these cans accumulated on the floor of the room and was carried by currents of air, and the feet of attendants, to that portion of the room used by the animals. It is almost certain that the food of the animals was contaminated as well. In this manner the animals ingested inhaled such quantities of lead as to completely spoil the experiment.

Analytical Results - March 3rd.

3 Guinea pigs - Pen No. 1.	2.10 - 2.10 - 2.55	
3 " " " " 2.	2.00 - 2.00 - 2.10	
3 " " " " 3.	1.60 - 2.00	Beaker broken analysis spoiled.

Analysis Repeated March 31 as Check.

1 Guinea Pig - Pen No. 1.	White buck, weight 1-11/16 lbs.	2.55
1 " " " " 2.	White and black female, weight 1-3/16 lbs.	2.10

As a result of the error in the manner of conducting this experiment, no conclusions may be drawn as to the quantity of lead which may have been absorbed from the leaded gasoline. It may be of some significance,

however, that the quantity of lead absorbed from the gasoline, if any, made no appreciable difference in the total lead obtained from all sources. Such variation as occurs in the entire group of animals may be explainable on the basis of variations in weight. It is certainly significant, that even under these adverse conditions, there was no demonstrable evidence of the poisoning of any one of these animals, unless the miscarriages be considered. This is of extremely doubtful significance, since such occurrences are not infrequent in a group of this number of animals in any environment.

MONKEYS

Monkey No. 1 Rhesus Male Weight 5-1/8 lbs. Jan. 19

Treated with 2 cc. Ethyl Gasoline daily.

Number of treatments 88.

This monkey is now lively, apparently perfectly well, is tame, playful, and in good condition in every way, except for some degree of irritation of the skin of his back.

In February he was somewhat ill, and lost his appetite. The weather was bad at this time and all the animals were exposed to too low a temperature for a few days. The animal lost weight at this time, dropping to 4-1/8 pounds. Subsequently he improved, regained weight slowly, and now weighs 4-13/16 pounds.

Blood examinations when received indicated the following conditions: Red count, 4,144,000; White count, 13,800; Haemoglobin, 85. Smears showed no variation from the normal appearance of the erythrocytes.

Examination of the blood has been made at regular intervals up to the present. Only slight variations of the erythrocytes have been seen.

The leucocytes have varied much more. The last examination, May 15th, is as follows: Red count, 4, 900,000; White count, 10,500; Haemoglobin, 90. Smears showed an occasional erythrocyte taking the basic stain to a slight degree. No stippling, and no other abnormality is found.

Monkey No. 2. Rhesus Female Weight 6-1/4 lbs. Jan. 19

Treated with 2 cc. Ethyl Gasoline daily.

Number of treatments 88.

This monkey is normal in every discernable way, except for the development of an elephantiasis of the vulva. She is lively, and playful, though she has not developed the tameness of the other.

She, too, was ill in February, lost a little weight, developed sniffles, and ate but poorly for several days. She regained the weight subsequently, apparently recovered entirely, weighing now 8-1/8 pounds.

The initial blood examinations showed the following results: Red count, 5,020,000; White count, 16,400; Haemoglobin, 90. Smears showed no evidence of any abnormality.

Blood examinations have been made on this animal. There has been no significant variation in the enumeration of the blood elements, nor has the blood picture developed any abnormalities. The last examination, May 15th, was as follows: Red count, 5,700,000; White count, 8,700; Haemoglobin, 90. Smears showed an occasional basophilic erythrocyte. No stippling found.

In April the animals concerned in the above experiments were moved into different quarters, which allow of no opportunity of exposure to lead in any way other than under controlled experimental conditions. Treatments are being continued to determine if symptoms and signs of poisoning can be produced by the experimental methods previously outlined.

THE HAZARD OF LEAD POISONING

FROM THE

HANDLING AND USING OF ETHYL GASOLINE

The interpretation of animal experiments in terms of human beings is at best a questionable proceedure. When one is determining the toxic properties of a general protoplasmic poison, a reasonable assurance exists as to the qualitative importance of the experiments. The quantitative value of such experiments is always a matter of doubt. This, because of certain variations in the physiological mechanisms of different organisms, and because of unavoidable variation in the manner and rate of introduction of the material in question, into the tissues of various animals.

The interpretation of the hazard existing from the handling and use of "Ethyl Gasoline", in terms of animal experimentation is doubly questionable, because it is impossible to duplicate the actual conditions under which such handling occurs. An attempt was made to err on the side of an increased exposure of animals over that likely to occur. Whether or not that was accomplished is a matter of judgment.

In this situation, the advisability of making observations in the actual field of operations, suggested itself months ago. Accordingly arrangements were made for the careful taking of histories of exposure, the making of careful physical examinations, and the analyses

of specimens of urine and faeces of a considerable number of men who had been exposed to actual conditions over a considerable period of time. The opportunity to do this was present in that employees of the General Motors Research Garage, and of the Dayton Power and Light Company, and of the Refiners Oil Company of Dayton, had been exposed to all of the conditions which could possibly bring danger of lead poisoning from the distribution and use of Ethyl Gasoline and from the use and mechanical care of cars using Ethyl Gasoline, and over a considerable period of time. (It must not be supposed that these men had been carelessly allowed to assume these dangers without any knowledge of them, or without medical observation at regular intervals. The fact remains, however, that the early methods of use and distribution of Ethyl Gasoline were of such a sort as to present hazards of such a magnitude as will never exist under the present methods of use and distribution.)

Full data is available as to the histories of exposure, the physical findings, and the clinical symptoms of these men. Analytical data will be presented on as many of them as are now available. The following table presents in brief the items of importance found in the analysis of these data.

Persons Examined

General Motors Research Garage	Mechanics	Handlers of Ethyl Gasoline	Drivers
5	1	1	3
Refiners Oil Co. at Dayton			
2	-	2	-
Dayton Power and Light Company			
23	5	2	16

History as to Exposure

Total Number Exposed	Not less than 2 yrs.	Not less than 1yr.	Less than 1 yr.
30	26	3	1

Symptoms appearing in Thirty Men exposed to Ethyl Gasoline and Exhuast Gas.

Head-Ache	Loss of Weight	Insom-nia	Disturb-ing dreams	Polyaria	Gastric Cramps	Digestive Disturbances	Weakness
1	1*	None	2**	None	None	1***	None

Notes: * This man lost weight following an attack of cholecystits.
** Both of these men gave a history of dreaming for years and admitted the condition only after leading questions.
*** This man gave a history of diarrhoea and fever, followed by constipation.

PHYSICAL SIGNS APPEARING IN THIRTY MEN EXPOSED

TO ETHYL GASOLINE AND EXHAUST GAS.

Pallor	Sub-normal Temperature.	Bradycardia	Sub-normal Blood Pressure.	Lead Line	Stippling	Low Haemoglobin
2	4 3 (97.6) 1 (97.2)	None	4 (1) 114-72 (1) 112-70 (1) 110-74 (1) 106-66	None	None	2

Notes: Of the two showing pallor, one has a chronic cholecystitis and the other has a history of tuberculosis of long standing.

The other findings are of no more frequent occurrence than may be seen in any group of men taken at random, and they are explainable on the basis of other physical findings such as very bad dental condition, existance of common colds, etc.

At the same time, sixty four men, at no time exposed to Ethyl Gasoline, have been questioned as to the details of their employment for the past several years and have been carefully examined. Specimens of urine and faeces have been obtained for analysis so as to furnish a comparison with the previously examined exposed men.

A detailed analysis of the data obtained from unexposed men as to their histories and the results of physical examinations would require too much space for the present needs. However, the data now available as to the results of the chemical examination of specimens of urine and faeces are appended hereto.

CONCLUSIONS

A careful consideration of the results of the examination of thirty men who have been exposed over a period of about two years, to one or more of the hazards arising from the general distribution and use of Ethyl Gasoline, fails to show any evidence of the appearance of either symptoms or signs of lead poisoning.

Appended hereto are data as to the analyses of urines and faeces. They are as yet incomplete and are submitted for what they are worth.

Analytical Data from Ten Men Exposed to Ethyl Gasoline

(Nos. 13, 14, 15 and 17 were also exposed to undiluted fluid containing tetraethyl lead and ethylene dibromide for a considerable period of time. See history)

Average Sample Urine (0.182 mg.
(1525 c.c. Urine

Average Sample Feces (0.519
(33.05 gm. Dried Feces

0.12 mg. per liter Urine
1.57 mg. per 100 gm. dried feces.

Sample	Weight dried feces in grams	mg.	Vol. Urine in c.c.	mg.
1	27.4	0.50	700	0.14
3	21.1	0.32	1200	0.17
4	11.1	0.11	3000	0.22
6	4.5	0.14	470	0.12
8	40.2	0.65	1200	0.17
11	29.8	0.32	1500	0.08
13	7.8	0.30	1400	0.10
14	117.3	1.91	2900	0.14
15	33.0	0.29	1350	0.56
17	38.3	0.65	1530	0.12

May 18, 1925.

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Analytical Data from Ten Control (Unexposed) Workmen.

Average Sample Urine (0.091 mg.
(1473 c.c. Urine

Average Sample Feces (0.38 mg.
(27.32 gm. Dried Feces

0.06 mg. per liter Urine

1.36 mg. per 100 gm. dried feces.

Sample	Weight dried feces in grams	mg.	Vol.Urine in c.c.	mg.
29	22.7	0.74	2200	0.14
68	35.6	0.32	1650	0.11
74	45.4	0.24	1300	0.15
77	50.0	0.22	1180	0.07
78	11.8	0.16	1850	0.15
80	18.3	0.22	1320	0.10
81	28.4	0.14	1400	0.07
82	7.8	0.18	1950	0.05
83	32.8	0.56	710	0.07
84	23.4	0.54	1170	Nil