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Tetra-ethyl Lead Poisoning *

A Clinical Analysis of a Series of Non-fatal Cases.

by

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Lead in various forms has been recognized as one of the ^{important} occupation poisons for a long time. The zealous study and the insistent presentation of the characteristics of the condition have outlined a clinical picture which is a matter of general medical instruction and knowledge, in spite of the controversial nature of certain diagnostic details. The manufacture and handling of tetra-ethyl lead, resultant upon its recent development for important industrial purposes, has brought about the appearance of a type of lead poisoning, which because of its unique character, is made the subject of the present paper.

Tetra-ethyl lead is a clear, heavy, (sp.g. about 1.62), oily liquid with a peculiar sweetish odor, which is somewhat volatile at ordinary temperatures. It is insoluble in either hot or cold water, but soluble in alcohol and acetone and miscible in all proportions with fats and oils. It decomposes in the presence of sunlight with the formation of crystalline tri-ethyl lead oxide, which in the presence of a halogen forms the tri-ethyl lead salt. Crude tetra-ethyl lead and old containers of tetra-ethyl lead are likely to show the presence of this oxide or the halogen salts. The salts are water soluble. They have a peculiar odor not wholly unlike that of tetra-ethyl lead, and when inhaled in even very low concentration they cause violent sneezing and a marked irritation of the mucous membranes. Tetra-ethyl lead is not immediately corrosive when applied to living tissues, but after exposure for some time necrosis results. If allowed to remain

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produced, but desquamation occurs after a day or two, leaving white and glistening patches. However, if removed from the skin (best done with kerosene) within a short time after its application, no harmful effect on the skin is produced.

It would be assumed that such a compound of lead is a general protoplasmic poison, and in fact chemists in general have regarded it as such. Observation and experimentation have confirmed the truth of this assumption, and have shown the extent of toxicity, the avenues of admission into the body, and the clinical features which develop in the course of the poisoning. The peculiarities of the poisoning are striking, so much so that the condition ^{often} bears little resemblance to any of the clinical types of lead poisoning except the infrequent lead encephalitis. Nevertheless, it cannot be doubted that the lead is the essential toxic agent in the compound. In fact, its toxicity is of the same order of magnitude as that of other well known compounds of lead. ✓ The peculiar symptoms and signs produced are due, in all likelihood, to the physical and chemical properties of the compound which permit of a more rapid absorption through the skin and lungs than is possible in the case of the more common lead compounds. More important, perhaps, its distribution in the tissues may be confidently expected to differ from that of the usual lead compounds, in that its solubility in fats predisposes its early localization in relatively high concentration in tissues of high fat content, such as adipose tissue, central nervous system, and liver.

Modes of Entrance

It has been shown experimentally that tetra-ethyl lead is capable of producing illness and death of animals when inhaled as a vapor, when absorbed through the skin, and when administered orally or intravenously. ✓ Under any one of these conditions death may be

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brought about in the course of three to six hours, though minimal lethal doses kill in from twenty four to seventy two hours. ordinarily. Even intravenous administration does not produce immediate or even quick death, unless injected in such quantities and at such a rate as to mechanically block large pulmonary vessels. (Tetra-ethyl lead is immiscible with blood and does not cause coagulation. It may well be that poisonous properties depend upon some degree of decomposition of the tetra-ethyl lead molecule.)

In man poisoning is produced as a result of the inhalation of the vapor of tetra-ethyl lead, and also as a result of skin absorption. It may be produced accidentally or carelessly by ingestion, but of tetra-ethyl lead in the industrial handling such a source of poisoning is not encountered to any important degree. Usually, illness in men has been the result of the combination of skin absorption and inhalation of vapor over a considerable period of time. (The inhalation of the dust of the tri-ethyl lead decomposition products of tetra-ethyl lead has also been seen to produce illness, which, under the conditions of observation, could not be differentiated from that due to tetra-ethyl lead alone.) However, an acute, even fatal, poisoning may result from ~~XXXXXXXX~~ exposure either to a high concentration of vapor for a comparatively short time ~~XXXXXXXXXXXXXXXXXXXXXXXXXXXX~~ (several working days) , or to a large quantity allowed to remain on a large skin surface .

Symptoms ~~and Signs.~~

Under conditions which allow of the absorption of tetra-ethyl lead in any manner, in sufficient quantity, an illness develops in which some or all of the following subjective symptoms appear:

~~XXXXXXXX~~ Insomnia. This is one of the earliest and most troublesome symptoms. It may be so severe as to prevent any sleep for days at a time, or it may cause only frequent waking. In severe cases, any sleep which

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with frequent twitchings of the body, frequent movements, and crying out. The complaint is frequently made by the patient that his mind is too active to allow sleep, and that when asleep or awake he is in a dream or dream-like state in which all kinds of grotesque and unusual situations arise. The attempt to sleep is more fatiguing than to remain active.

Nausea ~~and~~ Anorexia, and Vomiting. These symptoms are most pronounced in the early morning. A sickening taste, not described as metallic, contributes somewhat to the development of these symptoms. Such an individual contemplates breakfast with a positive aversion, though as the day goes on he feels better and often eats heartily and with relish in the evening. However, an attack of nausea and vomiting may be precipitated at any time by the odor of tetra-ethyl lead, or even other, to him, objectional odors.

Vertigo and Headache. Neither of these are pronounced in most cases, though something ~~approaching~~ approaching them, in the form of a dull, full feeling in the head is often complained of. Occasionally, however, the vertigo is strikingly in evidence.

Muscular weakness. Some degree of weakness is a constant finding, and is commonly a very persistent complaint. It does not appear until the insomnia and anorexia are well established, and appears to be due in most cases to inadequate ~~XXXXX~~ rest and food.

Itching of the skin is an occasional disturbing symptom.

Objective Signs.

The above symptoms are unvaryingly accompanied by the following signs.

Pallor. This is so uniform as to be impressive. It is not due to a blood destruction, but rather to a generally inadequate circulation brought about by a pronounced fall in blood pressure.

Subnormal Blood pressure. The blood pressure changes are seen early. They represent among the most reliable diagnostic signs.

The systolic pressure may ^{be} as low as eighty millimeters of mercury in

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a patient with a previously normal pressure. The diastolic pressure is relatively lower in almost every case, ~~XXXXXXXXXXXXXXXXXXXX~~ the pulse pressure being from fifty to seventy millimeters of mercury.

Subnormal Temperature. The temperature is extremely low in the early morning hours, often being as low as ninety six degrees, rarely being above ninety seven in affected persons. It ascends during the day but is usually subnormal throughout the entire twenty four hours.

Loss of weight is a constant finding, varying from slight to great decreases such as fifteen pounds in two or three weeks.

Tremor. A well defined and coarse tremor is seen in most cases. With this the reflexes are exaggerated, and the muscles, themselves, are commonly hyperirritable, responding easily to mechanical stimulation. Occasionally the tremor is the most striking sign. In such a case there is a continuous tremor, exaggerated when an attempt is made to control it, and increased greatly by sudden, unexpected noises or events. The sudden twitching of an arm or leg may arouse the subject from sleep or cause him to drop an object held in the hand.

Peripheral neuritis, with ~~paralysis~~ or anaesthesia, has not been seen in any of these cases
There is an increased respiratory rate, and ~~usually~~ a decreased pulse rate. *Paralysis*

Gastric and intestinal cramps are not an important item in the clinical picture. In the few cases in which they have appeared they have not been severe. They have never been the cause of initial complaint.

Neither constipation nor diarrhoea is seen often.

Blood Findings. There is no characteristic blood finding.

Haemoglobin determinations, carried out regularly on all patients have failed to yield any information. In one or two cases there has been a very slight diminution, but in no case has it been significant.

(Determinations made with Dare instrument.) There is little or nothing in the microscopic examination of the blood to ^{indicate} ~~suggest~~ destruction of the erythrocytes. Polychromatophilia and stippling are found in a high percentage of cases of slow absorption over a period of months, but

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^{is}~~was~~ almost uniformly absent. Even in the cases which show~~d~~^{are} polychromatophilia and stippling, (and these ~~were~~^{are} never pronounced blood pictures, such as are frequently seen in ordinary types of lead poisoning), there ^{is}~~was~~ no appreciable diminution of erythrocytes.

^{omit underlining} → Lead Line. The appearance of a lead line on the gums is not a constant, nor even a frequent finding. A lead line has been seen in several cases, and in two cases the line has been quite pronounced and characteristic. Yet this is not an early or important item in the diagnosis.

Urinary findings are meager except for ~~the determination of~~ the presence of lead. There is a constant hyperacidity of the urine in all severe cases, the urine remaining strongly acid to Methyl Red during the entire twenty four hours. Albumin does not appear in the urine of even severely poisoned individuals.

Lead Excretion. Lead is excreted in larger quantities than is seen in most cases of lead poisoning. Excretion occurs by way of both kidneys and alimentary tract. Usually the excretion in the faeces exceed that in the urine for a corresponding period of time. However, in one case, the urinary excretion uniformly exceeded that of the faeces. The quantity excreted in a twenty-four specimen of urine has varied from nil up to 8.4 mg of lead.

Clinical Types.

In mild cases of poisoning, where the exposure has been slight and brief, insomnia and anorexia, with a slight drop in blood pressure^{and to an extent} are frequently the only findings. In such a case ~~WAXXXX~~ the examination of the blood has failed to yield the slightest information. ~~INXXXXXX~~
 Instead of ^{sleeplessness}~~insomnia~~ the victim may complain of being disturbed in his sleep by frightful dreams. In the course of a few days this condition disappears almost entirely, though it may leave the blood pressure subnormal for from one to three weeks.

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In cases in which the symptoms are mild, but in which there has been a slight exposure over a considerable period of time (months) there is likely to be a change in the blood picture, in addition to the above symptoms. ^{A lead line has been seen in a few such cases, also.} Here careful examination of smears usually shows an occasional stippled ~~xxx~~ erythrocyte, without ^{the diminution} ~~a reduction~~ of haemoglobin, or the number of erythrocytes. The leucocyte count in such a case is commonly, though not constantly ~~xxxxxx~~ increased, ~~xxxxx~~ one or two thousand above the previous normal. Both the symptoms and the abnormalities in the blood picture tend to disappear quickly following cessation of exposure and ^{the instigation of} therapeutic measures.

In more severe cases the symptoms are more numerous. Loss of weight, insomnia, and anorexia are especially pronounced. With the improvement of ~~xxxxxx~~ of the patient, lassitude, weakness on exertion, and the subnormal ^{blood pressure and temperature} ~~xxxxxxxxxxxx~~ become the most prominent symptoms. The persistence of ~~xxxxx~~ this condition may be so striking as to simulate the chronic fatigue of low grade infectious diseases. In the course of ^{six to ten weeks} ~~time~~, however, all the symptoms disappear, and no ~~xxxxxxxxxx~~ residual effects can be found.

In ^{acute} ~~very severe~~ cases, a central nervous system involvement is seen at once to be the essential characteristic of the condition. The patient is irritable, "nervous", and is in a constant state of excitement, which may progress to such an extent as to render him maniacal. (No case of the writer's has presented such acute symptoms, but ^{two} ~~one~~ such cases have been seen by him. ^{these} observations made on ~~the one~~ cases are presented for the sake of completeness.) The mania resembles an alcoholic delirium very strikingly. In it the victim talks constantly and is in constant fear of animals or persons who are on the point of attacking him. His struggling to escape is continuous, and unless restrained or quieted in some fashion, he is likely to attempt to escape in any manner possible, even to leaping out of an upper window.

these conclusions, the treatment of tetra-ethyl lead poisoning need not differ from the treatment of lead poisoning ~~XXXXXXXXXX~~ of other types.

Accordingly a type of treatment was employed which has demonstrated its efficacy in several types of heavy metal poisoning. The experimental basis of the method ² and the clinical evidences ³ of its value appear elsewhere. ~~XXX~~ The principles underlying it are as follows;

(1) Heavy metals combine with and injure living tissue.

(2) The combination of heavy metal and tissue may be both prevented and broken by the presence of sufficient concentrations of salts of the light metals, in such a way as to restore the tissue to normal physical state, and free the heavy metal in soluble form for excretion.

(3) The symptoms of acid intoxication and edema, ~~XXXXXXXXXXXXXXXXXXXX~~ ~~XXXXXXXXXXXXXXXXXXXX~~, associated with heavy metal poisoning, especially of the acute type, may be combatted effectively by the same means.

The actual treatment consisted of the administration of mixtures of ~~XX~~ Sodium Bicarbonate or Sodium Citrate, Magnesium Oxide, and Calcium Carbonate in quantities sufficient to make and maintain neutrality of the urine. *Twenty to thirty grams of a mixture of such salts are required for this purpose.* In the more severe cases Magnesium Sulphate was added to the above list, given in small doses throughout the day in order to maintain a free diuresis. The bowels were kept open for the free secretion of lead by means of saline cathartics. ~~XXXXXXXXXX~~ Since none of the cases treated showed any evidence of the development of acute edema, large quantities of water and citrus fruit juices were administered.

No Narcotics were used to produce sleep. (It cannot be ~~XXX~~ emphasized too much that the use of opium compounds and chloral hydrate in this and in similar types of insomnia is an exceedingly dangerous

Therapeutic Results.

It was found that after a thorough alkalization the insomnia decreased in severity, usually disappearing in a few days. The appetite returned almost at once, and with it the subject ceased to lose weight. In several cases general weakness, nervous ~~XXXX~~ irritability, as evidenced by tremors and somewhat exaggerated reflexes, together with disturbing dreams, persisted for considerable periods of time. The low blood pressure also tended to persist. However, there was no increase of severity of symptoms, and no relapse into previously severe symptoms in a single case. It is possible, of course, that this resulted largely from cessation of exposure to tetra-ethyl lead, and from the rest and diversion occasioned by light out-of-door exercise and recreation. (None of these patients ~~XXXX~~ ^{was} put to bed for the reason that none of them was dangerously ill, and all of them maintained stoutly that they felt better ^{out of bed,} ~~when going about.~~)

On the other hand it is probably not without significance that none of the delayed effects of either ordinary lead poisoning or of this particular type of lead poisoning has appeared in any of these cases. Experimental evidence obtained in the study of these patients is to be made the subject of a later and more detailed paper, but on clinical evidence alone the writer feels justified in presenting the above method of treatment as the most satisfactory one which can now be offered. (It is the opinion of the writer that the beneficial effects of the administration of Sodium ~~Thiosulphate~~ ⁴ and Potassium Iodide in lead poisoning, ~~are explainable~~ ^{are explainable} on the basis of the principles above stated. It seems likely that a greater effect may be obtained from the use of light metal salts which are borne in much higher concentration than ~~these.~~ ^{these.}) The efficacy of these therapeutic methods in the acute maniacal types of tetra-ethyl lead

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